

filed

HARNESSE, DICKEY & PIERCE, P.L.C.

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Date: November 26, 1997

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

OK
11/26/97

EXPRESS MAILING CERTIFICATE

Applicants: Randal J. Kaufman, Steven W. Pipe and Kagehiro Amano

Serial No. (if any):

For: Inactivation Resistant Factor VIII

Docket: 2115001184USB

Attorney: DeAnn F. Smith

DT
12-26-97 pc
12-26-97 n+mp
1-26-98 pa

EH293851459US

"Express Mail" Mailing Label Number **EH 293 851 459 US**

Date of Deposit **November 26, 1997**

I hereby certify and verify that the accompanying return postcard, transmittal letter, 37-page patent application including at least one claim and abstract, and sixteen (16) sheets of informal drawings showing Figures 1A-16 are being deposited with the United States Postal Service "Express Mail Post Office To Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is (are) addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

Jeanette R. Fithian

Signature of Person Mailing Document(s)
Jeanette R. Fithian

09319093-04-1101



**LAHIVE
&
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L L P
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DAVID R. BURNS
JOHN S. CURRAN

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PETER W. DINI, Ph.D.
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LISA M. DIROCCO
JENNIFER K. ROSENFELD
JUDITH STONE-HULSLANDER, Ph.D.
ALLAN TAMESHTIT, Ph.D.
CATHERINE E. McPHERSON
ERIC F. WAGNER, Ph.D.
SHAHID HASAN, Ph.D.
ASHITA DOSHI, Ph.D.
JACOB G. WEINTRAUB

* Admitted in NY only
** Passed the Patent Bar Examination

May 9, 2001

RECEIVED

JUN 14 2001

TECH CENTER 1600/2900

BOX DAC

Commissioner for Patents
Washington, D.C. 20231

Re: U.S. Patent Application Serial No. 08/980,038
Applicants: Randal J. Kaufman, et al.
Title: *INACTIVATION RESISTANT FACTOR VIII*
Filed: November 26, 1997
Examiner: Celsa, B., Group Art Unit: 1654
Attorney Docket No.: UMV-1184CPCPA2

Dear Sir:

I enclose herewith for filing in the above-identified application the following:

1. Petition to Convert Continuing Prosecution Application Filed Under Rule 1.53(d) to a Continuation Application Under Rule 1.53(b) Pursuant to 37 C.F.R. 1.53(e);
2. Copy of prosecution history of U.S. Application Serial No. 08/980,038;
3. Check in the amount of \$130.00; and
4. A return postcard.

Please charge any deficiencies in late fees to our Deposit Account No. 12-0080. The undersigned requests any extensions of time necessary to respond. A duplicate of this sheet is enclosed.

I hereby certify that this correspondence is deposited with the United States Postal Service as first class mail in an envelope addressed to: **Box DAC**, Commissioner for Patents, Washington, DC 20231 on:

May 9, 2001
Date
DeAnn F. Smith
DeAnn F. Smith, Reg. No. 36,683

LAHIVE & COCKFIELD, LLP
Attorneys at Law

By *DeAnn F. Smith*
DeAnn F. Smith, Esq.
Registration No. 36,683
28 State Street
Boston, MA 02109
Telephone - 617-227-7400
Facsimile - 617-742-4214

Dated: May 9, 2001

Please type a plus sign (+) inside this box



PTO/SB/29 (12/97)
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE



Under the Paperwork Reduction Act of 1995, no persons are required to respond to a collection of information unless it displays a valid OMB control number.

CONTINUED PROSECUTION APPLICATION (CPA) REQUEST TRANSMITTAL

Submit an original, and a duplicate for fee processing
(Only for Continuation or Divisional applications under 37 CFR 1.53(d))

CHECK BOX, if applicable:

☐ DUPLICATE



Address to:

Commissioner for Patents
Box CPA
Washington, D.C. 20231

Attorney Docket No.

UMV-1184CPCPA2

First Named Inventor

Randal J. Kaufman

Express Mail Label No.

EL 745 889 166 US

Total Pages

CERTIFICATION UNDER 37 CFR 1.10

Date of Deposit: April 11, 2001

Mailing Label Number: EL745 889 166 US

I hereby certify that this Continued Prosecution Application (CPA) Request Transmittal and the documents referred to as attached therein are being deposited with the United States Postal Service on the date indicated above in an envelope as "Express Mail Post Office to Addressee" service under 37 CFR 1.10 and addressed to Commissioner for Patents, Box CPA, Washington, D.C. 20231.

Nelson F. Barros

Name of Person Mailing Paper

Signature of Person Mailing Paper

This is a request for a ☒ continuation or ☐ divisional application under 37 CFR 1.53(d), (continued prosecution application (CPA)) of prior application number 08/980,038 (Cnfrm No. 6548), filed on November 26, 1997, entitled INACTIVATION RESISTANT FACTOR VIII

NOTES

FILING QUALIFICATIONS: The prior application identified above must be a nonprovisional application that is either: (1) complete as defined by 37 CFR 1.51(b) and filed on or after June 8, 1995, or (2) the national stage of an international application in compliance with 35 U.S.C. 371 and filed on or after June 8, 1995.

C-I-P NOT PERMITTED: A continuation-in-part application cannot be filed as a CPA under 37 CFR 1.53(d), but must be filed under 37 CFR 1.53(b).

EXPRESS ABANDONMENT OF PRIOR APPLICATION: The filing of this CPA is a request to expressly abandon the prior application as of the filing date of the request for a CPA. 37 CFR 1.53(b) must be used to file a continuation, divisional, or continuation-in-part of an application that is not to be abandoned.

ACCESS TO PRIOR APPLICATION: The filing of this CPA will be construed to include a waiver of confidentiality by the applicant under 35 U.S.C. 122 to the extent that any member of the public who is entitled under the provisions of 37 CFR 1.14 to access to, copies of, or information concerning, the prior application may be given similar access to, copies of, or similar information concerning, the other application or applications in the file jacket.

35 U.S.C. 120 STATEMENT: In a CPA, no reference to the prior application is needed in the first sentence of the specification and none should be submitted. If a sentence referencing the prior application is submitted, it will not be entered. A request for a CPA is the specific reference required by 35 U.S.C. 120 and to every application assigned the application number identified in such request, 37 CFR 1.78(a).

1. ☐ Enter the unentire amendment previously filed on _____ under 37 CFR 1.116 in the prior nonprovisional application.
2. ☐ A preliminary amendment is enclosed.

(Page 1 of 2)



Burden Hour Statement: This form is estimated to take 0.4 hours to complete. Time will vary depending upon the needs of the individual case. Any comments on the amount of time you are required to complete this form should be sent to the Chief Information Officer, Patent and Trademark Office, Washington, D.C. 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Assistant Commissioner for Patents, Box CPA, Washington, D.C. 20231.

3. This application is filed by fewer than all the inventors named in the prior application, 37 CFR 1.53(d)(4).

a. ☐ **DELETE** the following inventor(s) named in the prior nonprovisional application:

b. ☐ The inventor(s) to be deleted are set forth on a separate sheet attached hereto.

4. ☐ A new power of attorney or authorization of agent (PTO/SB/81) is enclosed.

5. ☐ Information Disclosure Statement (IDS) is enclosed:

a. ☐ PTO 1449

b. ☐ Copies of IDS Citations

	NUMBER OF CLAIMS FILED			NUMBER EXTRA
TOTAL	56	MINUS	20	= 36
INDEP.	5	MINUS	3	= 2
<input type="checkbox"/> MULTIPLE DEPENDENT CLAIMS				

SMALL ENTITY

RATE	FEE
x 9 =	\$324.00
x 40 =	\$ 80.00
+135 =	\$ 0.00
BASIC FEE	\$355.00
TOTAL	\$759.00

OTHER THAN A
SMALL ENTITY

RATE	FEE
x 18 =	\$ 0.00
x 80 =	\$ 0.00
+ 270 =	\$ 0.00
BASIC FEE	\$ 0.00
TOTAL	\$ 0.00

OR

OR

6. Small entity status

a. ☐ A small entity statement is enclosed.

b. ☒ A small entity statement was filed in the prior nonprovisional application and such status is still proper and desired.

c. ☐ Is no longer claimed.

7. The Commissioner is hereby authorized to credit overpayments or charge the following fees to Deposit Account No. 12-0080:

a. ☒ Fees required under 37 CFR 1.16.

b. ☒ Fees required under 37 CFR 1.17.

c. ☒ Fees required under 37 CFR 1.18.

8. ☒ A check in the amount of \$759.00 is enclosed.

9. ☒ Other: ... Request for Three-Month Extension of Time, including a check for \$445.00 to cover the appropriate fee...

NOTE:

The prior application's correspondence address will carry over to this CPA UNLESS a new correspondence address is provided below.

10. NEW CORRESPONDENCE ADDRESS

☒ Customer Number or Bar Code Label

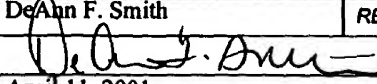
000959

(Insert Customer No. or Attach bar code label here)

or ☐ Correspondence address below

NAME	DeAnn F. Smith				
	LAHIVE & COCKFIELD, LLP				
ADDRESS	28 State Street				
CITY	Boston	STATE	MA	ZIP CODE	02109
COUNTRY	USA	TELEPHONE	(617) 227-7400	FAX	(617) 742-4214

11. SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT REQUIRED

NAME	DeAnn F. Smith	REG. NO.	36,683
SIGNATURE			
DATE	April 11, 2001		



Attorney Docket No. 2115S-001184USB

ART UNIT 1654
EXAMINER B. Celsa
INVENTOR(S) Randal J. Kaufman et al.
SERIAL NUMBER 08/980,038
FILED November 26, 1997
FOR Inactivation Resistant Factor VIII

**RESPONSE TRANSMITTAL AND
EXTENSION OF TIME REQUEST
(IF REQUIRED)**

DT
11-29-98pc

THE COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D. C. 20231

Sir:

FEE CALCULATION FOR ENCLOSED RESPONSE and EXTENSION REQUEST (if any)									
	Claims Remaining		Highest No. Previously Paid		Number Extra		Rate		Additional Fee
Total Claims	54	-	94	=	0	x	\$22.00	=	\$0.00
Independent Claims	5	-	8	=	0	x	\$82.00	=	\$0.00
Surcharge For Multiple Dependent Claim First Added							+\$270.00	=	
<input type="checkbox"/> Applicant requests a _____ month extension of time for response to the outstanding Office Action. The large entity fee is									
TOTAL									\$0.00
<input type="checkbox"/> SMALL ENTITY STATUS (If applicable, divide TOTAL by 2)									
<input type="checkbox"/> Verified Statement enclosed, if not previously filed.									
<input type="checkbox"/> Reduction for Extension Fee of _____ months already paid									
<input type="checkbox"/> OTHER:									
TOTAL									\$0.00

☐ A check is enclosed to cover the fees as calculated above.

☐ The fees calculated above are to be charged to Deposit Account No. 08-0750.

If for some reason applicant has not requested a sufficient extension of time and/or has not paid a sufficient fee for this response and/or for the extension of time necessary to prevent the abandonment of this application, please consider this as a Request for an Extension for the required time period and/or an authorization to charge our Deposit Account No. 08-0750 for any fee which may be due. A duplicate copy of this sheet is enclosed.

HARNESS, DICKEY & PIERCE, P.L.C.

P. O. Box 828
Bloomfield Hills, Michigan 48303
(248) 641-1600

By: DeAnn F. Smith
DeAnn F. Smith
Reg. No. 36,683

I hereby certify that this letter, the response attached hereto and, if enclosed, the small entity verification are being deposited with the United States Postal Service as first class mail in an envelope addressed to Commissioner of Patents and Trademarks, Washington, D.C. 20231, on October 29, 1998.

By: DeAnn F. Smith



JOHN A. LAHIVE, JR. (1928-1997)
THOMAS V. SMURZYNSKI
RALPH A. LOREN
GIULIO A. DeCONTI, JR.
ANN LAMPORT HAMMITTE
ELIZABETH A. HANLEY
AMY BAKER MANDRAGOURAS
ANTHONY A. LAURENTANO
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RICHANAND
MICHAEL PHILLIPPS

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PATENT AGENTS
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CATHERINE E. McPHERSON
ERIC F. WAGNER, Ph.D.
SHAHID HASAN, Ph.D.
ASHITA DOSHI, Ph.D.
JACOB G. WEINTRAUB

* Admitted in NY only
** Passed the Patent Bar Examination

April 11, 2001

BOX CPA
Commissioner for Patents
Washington, D.C. 20231

Re: U.S. Patent Application Serial No. 08/980,038 (CPA filed herewith)
Applicants: Randal J. Kaufman, et al.
Title: *INACTIVATION RESISTANT FACTOR VIII*
Filed: November 26, 1997
Examiner: Celsa, B., Group Art Unit: 1654
Attorney Docket No.: UMV-1184CPCPA2

Dear Sir:

I enclose herewith for filing in the above-identified application the following:

1. Continued Prosecution Application (CPA) Request Transmittal (in duplicate);
2. Request for Three-Month Extension of Time;
3. Checks in the amount of \$759.00 (appln fee) and \$455.00(extension fee); and
4. A return postcard.

Please charge any deficiencies in late fees to our Deposit Account No. 12-0080. The undersigned requests any extensions of time necessary to respond. A duplicate of this sheet is enclosed.

"Express Mail" mailing label number	EL 745 889 166 US
Date of Deposit	April 11, 2001
I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to BOX CPA, Assistant Commissioner for Patents, Washington, DC 20231	
<i>Nelson Barros</i>	
Nelson F. Barros	
Please Print Name of Person Signing	

LAHIVE & COCKFIELD, LLP
Attorneys at Law

By *DeAnn F. Smith*
DeAnn F. Smith, Esq.
Registration No. 36,683
28 State Street
Boston, MA 02109
Telephone - 617-227-7400
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EL745889166US



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U.S.A.

Date: November 26, 1997

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(248) 641-0270

Hon. Commissioner of Patents and Trademarks
Washington, D. C. 20231

Re: Inventors: Randal J. Kaufman, Steven W. Pipe and Kagehiro Amano
For: Inactivation Resistant Factor VIII

Atty. Docket No.: 2115001184USB



Sir:

Transmitted herewith for filing is the above referenced patent application.

1. ☒ formal / sixteen (16) informal sheets of drawings showing
Figures 1A-16 are enclosed.
2. ☐ A Verified Statement Claiming Small Entity Status is enclosed.
- 3a. ☐ A check is enclosed to cover the fees as calculated below. The Commissioner
is hereby authorized to charge any additional fees which may be required, or
credit any overpayment to Deposit Account No. 08-0750. A duplicate copy of
this document is enclosed.
- 3b. ☒ The fees calculated below will be paid within the time allotted for completion of
the filing requirements.
- 3c. ☐ The fees calculated below are to be charged to Deposit Account No. 08-0750.
The Commissioner is hereby authorized to charge any additional fees which
may be required, or credit any overpayment to said Deposit Account. A
duplicate copy of this document is enclosed.

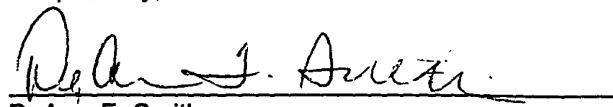
FILING FEE	Number	Number	Basic Fee
CALCULATION	Filed	Extra	Rate
Total Claims	40 - 20 =	20 x	\$22.00 = \$440.00
Independent Claims	4 - 3 =	1 x	\$82.00 = \$82.00
Multiple Dependent Claim(s) Used			\$270.00 =
FILING FEE - NON-SMALL ENTITY			\$1,312.00
FILING FEE - SMALL ENTITY: Reduction by 1/2			
<input type="checkbox"/> Verified Statement enclosed.			
<input type="checkbox"/> Verified Statement filed in priority application.			
Assignment Recordal Fee (\$40.00)			
37 C.F.R. §1.17(k) Fee (non-English application)			
TOTAL			

Date: November 26, 1997

4. ☐ An Assignment of the invention is enclosed. The required cover sheet under 37 C.F.R. §3.11, §3.28 and §3.41 is attached.
5. ☒ A signed Oath/Declaration ☐ is enclosed ☒ will be filed in accordance with 37 C.F.R. 1.63.
6. ☒ **Foreign Priority:** Priority based on PCT International Application No. PCT/US97/06563, filed April 24, 1997 (which is a continuation-in-part of U.S. Serial No. 60/016,117, filed April 24, 1996 and U.S. Serial No. 60/017,785, filed May 15, 1996, see 9. below), is claimed.
7. ☐ A copy of the above referenced priority document ☐ is enclosed ☐ will be filed in due course, pursuant to 35 U.S.C. §119(a)-(d).
8. ☐ Because the enclosed application is in a non-English language, a verified English translation for examination purposes of same ☐ is enclosed ☐ will be filed as soon as it is available.
9. ☒ **Provisional Application Priority:** Priority based on United States Provisional Application No. 60/016,117, filed April 24, 1996 and United States Provisional Application No. 60/017,785, filed May 15, 1996, is claimed under 35 U.S.C. §119(e).
10. ☐ A Preliminary Amendment is enclosed.
11. ☐ An Information Disclosure Statement, _____ sheets of PTO Form 1449, and _____ patent(s)/publications/documents are enclosed.
12. ☐ An Establishment of Assignee's Right To Prosecute Application Under 37 C.F.R. § 3.73(b), and Power Of Attorney is enclosed.
13. ☒ An Express Mailing Certificate is enclosed.
14. ☐ Other _____

Attention is directed to the fact that the address of this firm has been designated as the correspondence address for this application.

Respectfully,


DeAnn F. Smith
Reg. No. 36,683

2115-00118414-10

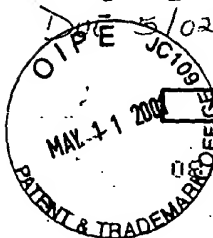
HParts

2010 ml

5/02/98



UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231



APPLICATION NUMBER	FILING/RECEIPT DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO./TITLE
05/980,038	11/26/97	KAUFMAN	R 2115001184US

0362/0302

HARNES DICKEY & PIERCE
ATTORNEYS AND COUNSELLORS
PO BOX 828
BLOOMFIELD HILLS MI 48303

NOT ASSIGNED

1654

DATE MAILED:

03/02/98

NOTICE TO FILE MISSING PARTS OF APPLICATION

Filing Date Granted

An Application Number and Filing Date have been assigned to this application. However, the items indicated below are missing. The required items and fees identified below must be timely submitted ALONG WITH THE PAYMENT OF A SURCHARGE for items 1 and 3-6 only of \$ 150.00 for a ☒ large entity ☐ small entity in compliance with 37 CFR 1.27. The surcharge is set forth in 37 CFR 1.16(e). Applicant is given TWO MONTHS FROM THE DATE OF THIS NOTICE within which to file all required items and pay any fees required above to avoid abandonment. Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136(a).

If all required items on this form are filed within the period set above, the total amount owed by applicant as a ☒ large entity ☐ small entity (verified statement filed), is \$ 1742.00

☒ 1. The statutory basic filing fee is:

- ☒ missing.
☐ insufficient.

Applicant must submit \$ 790.00 to complete the basic filing fee and/or file a verified small entity statement claiming such status (37 CFR 1.27).

☒ 2. Additional claim fees of \$ 522.00, including any multiple dependent claim fees, are required.

Applicant must either submit the additional claim fees or cancel additional claims for which fees are due.

☒ 3. The oath or declaration:

- ☐ is missing.
☐ does not cover the newly submitted items.
☐ does not identify the application to which it applies.
☐ does not include the city and state or foreign country of applicant's residence.

An oath or declaration in compliance with 37 CFR 1.63, including residence information and identifying the application by the above Application Number and Filing Date is required.

☐ 4. The signature(s) to the oath or declaration is/are:

- ☐ missing.
☐ by a person other than inventor or person qualified under 37 CFR 1.42, 1.43, or 1.47.

A properly signed oath or declaration in compliance with 37 CFR 1.63, identifying the application by the above Application Number and Filing Date, is required.

☐ 5. The signature of the following joint inventor(s) is missing from the oath or declaration:

An oath or declaration listing the names of all inventors and signed by the omitted inventor(s), identifying this application by the above Application Number and Filing Date, is required.

☐ 6. A \$ processing fee is required since your check was returned without payment (37 CFR 1.21(m)).

☐ 7. Your filing receipt was mailed in error because your check was returned without payment.

☐ 8. The application does not comply with the Sequence Rules.

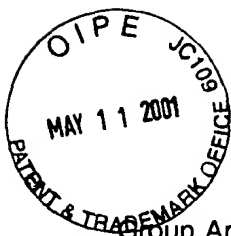
See attached "Notice to Comply with Sequence Rules 37 CFR 1.821-1.825."

☐ 9. OTHER:

Direct the response and any questions about this notice to "Attention: Box Missing Parts."

A copy of this notice MUST be returned with the response.

Terry Dyer
Customer Service Center
Initial Patent Examination Division (703) 308-1202



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

PATENT

Attorney Docket: 2115S-001184USB

Group Art Unit: 1654)
Examiner:)
Inventor(s): Randal J. Kaufman et al.)
Serial No.: 08/980,038)
Filed: November 26, 1997)
For: Inactivation Resistant)
Factor VIII)

RESPONSE TO NOTICE TO
FILE MISSING PARTS; and
REQUEST FOR ONE-MONTH
EXTENSION OF TIME

Attn: Box Missing Parts

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231 on May 26, 1998.

By

Randal J. Kaufman

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

DT
6-20-98
9-20-98

Sir:

In response to the Notice To File Missing Parts Of Application - Filing Date Granted mailed March 2, 1998 (copy enclosed) for which the two-month shortened period for response was set to expire May 2, 1998, Applicants hereby request a one-month extension of time in which to respond and submit a check herewith for the appropriate fee.

Enclosed are two (2) originally signed Declarations and Powers of Attorney, one executed by inventor Randal J. Kaufman and the other executed by inventors Steven W. Pipe and Kagehiro Amano.

Also, enclosed herewith for recordal is an Assignment of this application with attached coversheet. A check is enclosed to cover the fees associated with the assignment recordal.

Attorney Docket: 2115S-001184USB
Serial No. 08/980,038

In addition, enclosed herewith is a verification of Applicants' small entity status and an Establishment's Of Assignee's Right To Prosecute Application Under 37 C.F.R. §3.73(b), and Power of Attorney.

Applicants enclose a check in the total amount of \$816.00, which covers the one-month extension of time fee of \$55.00, the late-filing surcharge of \$65.00, the patent application filing fee of \$395.00, the additional claims fee of \$220.00, the additional independent claim fee of \$41.00 and the Assignment recordal fee of \$40.00.

If for some reason, Applicants have not paid a sufficient fee to prevent the abandonment of this application, please charge Deposit Account No. 08-0750 for any further fees which may be due. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

Dated: 5/26/98

By: DeAnn F. Smith
DeAnn F. Smith
Reg No. 36,683

Harness, Dickey & Pierce, P.L.C.
P.O. Box 828
Bloomfield Hills, Michigan 48303
(248) 641-1600

DFS/gmp
Enclosures



**UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office**

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/980,038	11/26/97	KAUFMAN	R 2115000184US

HARNES DICKEY & PIERCE
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HM11/0930

EXAMINER

CELSA, E

ART UNIT

PAPER NUMBER

1654

DATE MAILED: 09/30/98

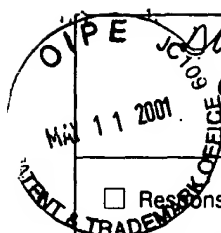
**Please find below and/or attached an Office communication concerning this application r
proceeding.**

Commissioner of Patents and Trad marks

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9/30/98



Due 10/30/98

Office Action Summary

Application No. 08/980,038	Applicant(s) Kaufman et al.
Examiner Bennett Celsa	Group Art Unit 1654

- ☐ Responsive to communication(s) filed on _____.
- ☐ This action is **FINAL**.
- ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire one month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

- ☒ Claim(s) 1-9 and 17-101 is/are pending in the application.
- Of the above, claim(s) _____ is/are withdrawn from consideration.
- ☐ Claim(s) _____ is/are allowed.
- ☐ Claim(s) _____ is/are rejected.
- ☐ Claim(s) _____ is/are objected to.
- ☒ Claims 1-9 and 17-101 are subject to restriction or election requirement.

Application Papers

- ☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- ☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
- ☐ The specification is objected to by the Examiner.
- ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- ☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
- ☐ received.
- ☐ received in Application No. (Series Code/Serial Number) _____.
- ☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

- ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- ☐ Notice of References Cited, PTO-892
- ☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
- ☐ Interview Summary, PTO-413
- ☐ Notice of Draftsperson's Patent Drawing Review, PTO-948
- ☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

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DETAILED ACTION

Claims 1-9 and 17-101 are currently pending. Claims 10-16 were canceled by preliminary amendment and new claims 41-101 were added.

The present application is a continuation application (and not a 371) of PCT/US97/06563, since the prerequisites for filing under 35 USC 371 were not met.

Election/Restriction

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:
 - I. Claims 1-4 and 8, drawn to a 309 modified FVIII analog proteins and pharmaceuticals thereof, classified in class 514 and 530, subclasses 2+ and 350+, respectively.
 - II. Claims 5-7 and 9, drawn to a recombinant method of making Group I proteins, classified in class 435, subclass 69.1+.
 - III.. Claims 17, 20-23 and 27, drawn to a B/VW/ 740 and A2/A3 spacer FVIII protein analog and pharmaceutical thereof classified in classes 514 and 530, subclass 2+ and 350+, respectively.
 - IV.. Claims 24-26 and 28, drawn to a recombinant method of making Group III proteins, classified in class 435, subclass 69.1+.
 - V.. Claims 29-31, drawn to a method of increasing the binding of a Group III protein in plasma using an antibody, classified in class 424, subclass 130.1+..

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- VI. Claims 32 and 36, drawn to a thrombin activated factor VIII heterodimer protein and a pharmaceutical thereof, classified in class 514 and 530, subclasses 2+ and 350+, respectively.
- VII.. Claims 33-35 and 37, drawn to a recombinant method of making the Group VI proteins, classified in class 435, subclass 69.1+.
- VIII. Claims 38-40, drawn to a method of increasing the binding of a Group VI protein using an antibody, classified in class 424, subclass 130.1+..
- IX.. Claims 41-44 and 48, drawn to a 309/336/562 factor FVIII analog protein, classified in class 514 and 530, subclasses 2+ and 350+, respectively.
- X.. Claims 45-47 and 49, drawn to a recombinant method of making a Group IX protein, classified in class 435, subclass 69.1+..
- XI.. Claims 18, 50-54 and 58, drawn to a B/VW/336/562/740 and A2/A3 spacer FVIII protein analog , classified in classes 514 and 530, subclass 2+ and 350+, respectively.
- XII.. Claims 55-57 and 59, drawn to a recombinant method of making a Group XI protein, classified in class 435, subclass 69.1+.
- XIII.. Claims 60-62, drawn to a method of increasing Group XII binding using an antibody, classified in class 424, subclass 130.1+

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- XIV.. Claims 19, 63-67 and 71, drawn to a B/VW/309/740 and A2/A3 spacer FVIII protein analog and a pharmaceutical composition thereof, classified in classes 514 and 530, subclass 2+ and 350+, respectively.
- XV.. Claims 68-70 and 72, drawn to a recombinant method of making a Group XIV protein, classified in class 435, subclass 69.1+.
- XVI.. Claims 73-75, drawn to a method of increasing the binding of a Group XIV protein using an antibody, classified in class 424, subclass 130.1+.
- XVII. Claims 76-80, 84 and 90, drawn to a B/VW/309/336/562/740 and A2/A3 spacer FVIII protein analog and a pharmaceutical composition thereof, classified in classes 514 and 530, subclass 2+ and 350+, respectively.
- XVIII. Claims 81-83 and 85, drawn to a recombinant method of making Group XVII proteins, classified in class 435, subclass 69.1+.
- XIX. Claims 86-88, drawn to a method of increasing the binding of a Group XVIII protein using an antibody, classified in class 424, subclass 130.1+.
- XX. Claims 89, 91-94, 98, 100 and 101 drawn to a B/VW/336/562/740 and A2/A3 spacer FVIII protein analog/antibody conjugate and a pharmaceutical composition thereof, classified in classes 424 subclass 130.1+.
- XXI. Claims 95-97 and 99, drawn to a recombinant method of making a Group XX protein, classified in class 435, subclass 69.1+.

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2. The inventions are distinct, each from the other because of the following reasons:

Inventions (I and II) and (III and IV) and (VI and VII) and (IX and X) and (XI and XII) and (XIV and XV) and (XVII and XVIII) and (XX and XXI) are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)).

In the instant case the products as claimed can be made by another and materially different process such as by solid or liquid phase peptide syntheses.

3. The protein compounds of Groups I, III, VI, IX, XI, XIV, XVII and XX are directed to patentably distinct proteins due to differences in structure including, but not limited to, differences in amino acid content and/or length and/or the presence of nonconservative substitutions and/or deletions and/or differences in secondary structure (e.g. cyclic) and/or the presence of an antibody conjugate; and further expected differences in physicochemical properties resulting from structural differences and/or differences in method of manufacture e.g. by use of different recombinant constructs. Further, the amino sequence searches of relevant databases as well as bibliographic searches of the proteins within the above groups is necessarily different and individually burdensome due to the divergent nature of each Group search.

4. The recombinant methods of Groups II, IV, VII, X, XII, XV, XVIII and XXI represent patentably distinct methods since each method is directed to the syntheses of a different protein and further requires unique recombinant constructs (e.g. vectors, plasmid, hosts etc). The

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differences among the methods of the different groups would necessitate different and individually burdensome bibliographic and sequences searches for each method

5. The methods of increasing the binding of different proteins utilizing an antibody in Groups V, VIII, XIII, XVI, and XIX are patentably distinct due to differences in the method objectives and/or expected generic differences in antibody specificity and other physicochemical properties..

6. Because these inventions are distinct for the reasons given above and:

- a. have acquired a separate status in the art as shown by their different classification;
- b. require separate literature and/or sequence searches; and
- c. because of their recognized divergent subject matter; restriction for examination purposes as indicated is proper.

7. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a petition under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(I).

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General information regarding further correspondence

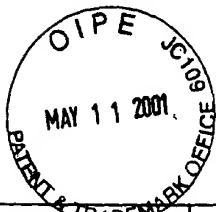
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Celsa whose telephone number is (703) 305-7556.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can be reached at (703)308-0254.

Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Bennett Celsa


September 29, 1998



**UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office**

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Washington, D.C. 20231

(TN)

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/500,000	11/25/97	KALIFMAN	R 211500118408

UNLESS INDICATED BY THE
OFFICE, THIS APPLICATION IS
FOR EXAMINATION
BLDGFIELD #1116-113-45311

RM22/0121

EXAMINER

TELSA.B

ART UNIT PAPER NUMBER

1554

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DATE MAILED: 01/21/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

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Office Action Summary

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Application No. 08/980,038	Applicant(s) Kaufman et al.
Examiner Bennett Celsa	Group Art Unit 1654

- ☐ Responsive to communication(s) filed on _____.
- ☐ This action is **FINAL**.
- ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

- ☒ Claim(s) 17-23, 27, 32, 36, and 102-145 is/are pending in the application.
- Of the above, claim(s) 18, 19, 32, 36, 102-106, 108, 109, 114-119, and 121 are withdrawn from consideration.
- ☐ Claim(s) _____ is/are allowed.
- ☒ Claim(s) 17, 20-23, 27, 107, 110-113, and 120 is/are rejected.
- ☐ Claim(s) _____ is/are objected to.
- ☐ Claims _____ are subject to restriction or election requirement.

Application Papers

- ☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- ☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
- ☐ The specification is objected to by the Examiner.
- ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- ☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
- ☐ received.
- ☐ received in Application No. (Series Code/Serial Number) _____.
- ☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).
- *Certified copies not received: _____.
- ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

- ☒ Notice of References Cited, PTO-892
- ☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 5-7
- ☐ Interview Summary, PTO-413
- ☐ Notice of Draftsperson's Patent Drawing Review, PTO-948
- ☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

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DETAILED ACTION

Claims 17-23, 27, 32, 36 and 102-145 are currently pending.

Claims 18-19, 32, 36, 102-106, 108-109, 114-119 and 121-145 are withdrawn from consideration as being directed to a nonelected invention.

Claims 17, 20-23, 27, 107, 110-113 and 120 are under consideration.

Election/Restriction

1. Applicant's election with traverse of the Group III invention (claims 17, 20-23 and 27) in Paper No. 10 is acknowledged. The traversal is on the ground(s) that Group III and VI should be examined together since they are not independent and distinct. This is not found persuasive for the reasons recited in the restriction requirement e.g. the proteins comprise different length and content of amino acids (e.g., different structure) and different physicochemical characteristics; means of manufacture (e.g. different recombinant constructs); different use etc. Applicant further argues that claim 32 is further claiming the "thrombin activated protein of claim 17" and thus are neither independent or distinct. However, it is clear that claim 17 requires different substitutions (e.g. Arg 740) and deletions (e.g. Vw binding site) not required by the protein of claim 32 and claim 32 requires a functional limitation which doesn't necessitate the modifications of claim 17. In other words Claims 17 and 32 encompass different protein structure and/or conformations and/or properties as pointed out in the restriction. Applicant further argues that there is not a serious burden of searching both the Group III and VI inventions due to similarities in classification. However, as pointed out in the restriction requirement, different literature and/or

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sequence searches would result in a burdensome search especially due to the above recited difference in amino acid structure, function, properties and manufacture of the different proteins within groups III and VI. Accordingly, Groups III and VI will not be grouped together. Applicant further argues that that claims 18 and 19 should be examined with Groups III and VI as being dependent on independent claim 17 and further defining the protein of claim 17. However, as again noted, the restriction provides reasons e.g. as to differences among protein structure (e.g. amino acid content and/or length), physicochemical properties, method of manufacture would differ among the proteins of Groups III, VI, XI (claim 18) and XIV (claim 19) as to result in independent and/or distinct proteins for restriction. Applicant further argues that claim 17 is a "linking claim" without explanation.. It is not understood how claim 17 is viewed by applicant as a means of linking proteins which possess different protein structure, properties and means of manufacture. Linking claims, with regard to restriction, usually is applicable with regard to composition not individual compounds. Accordingly, applicant's bare assertion of a linking claim, without further explanation, is not found persuasive. The requirement is still deemed proper and is therefore made FINAL.

2. The election of Group III (claims 17, 20-23 and 27). It is noted that new claims 107, 110-113 and 120 read on the elected invention.
3. Newly submitted claims 122-145 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Inventions III, VI, XI (claim 18) and XIV (claim 19) and claims 122-145 are related as product and process of use.

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The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the process for using the product as claimed can be practiced with another materially different product since the any of the proteins of Groups III, VI, XI and XIV can be used as well as the use of whole blood transfusions or factor VIII concentrates. Additionally, the product as claimed can be used in a materially different process of using that product such as the use in generating antibodies, diagnostic use and in affinity purification of factor VIII protein. The election of group III has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 122-145 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03. However, it is noted that in accordance with U.S. practice, upon the allowance of a compound claim within an elected compound invention, the Examiner will *consider rejoinder of* method of use claims which are commensurate in scope to the allowed subject matter pursuant to MPEP 821.04 Rejoinder

4. Accordingly:

a. Claims 17-23, 27, 32, 36 and 102-145 are pending.

B. Claims 17, 20-23, 27, 107, 110-113 and 120 are under consideration.

C. Claims 18-19, 32, 36, 102-106, 108-109, 114-119 and 121-145 are withdrawn from consideration as being directed to a nonelected invention.

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Sequence Rule Compliance

It is noted that the present application contain nucleotides and peptides within the purview of the Sequence Rules (e.g. see specification page 23). Accordingly, attached is a "Notice to Comply With the Sequence Listing" setting *an extendable one month period for response*.

Drawings

5. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 17, 20-23, 27, 107, 110-113 and 120 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In claims 17 and 107, the structure of the human factor FVIII polypeptide which is modified to attain the "procoagulant-active FVIII protein) is indefinite. One needs to know the starting point (e.g. the initial polypeptide structure) in order to determine a final product which would infringe or not infringe the claim. Thus, the metes and bounds of the final protein are not known if the metes and bounds of the starting polypeptide are not described.

B. In claims 17 and 107, the term "the B domain" lacks antecedent basis.

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C. In claims 17 and 107, the term "the von Willebrand factor binding site" lacks antecedent basis.

D. In claims 17 and 107, the term "the A2- and A3- domains" lack antecedent basis.

E. In claims 17 and 107, the phrase "a mutation at Arg740" lacks metes and bound as to what the metes and bounds of such mutations are. Do mutations include a deletion of Arg740 ? Only substitutions of Arg740 ? A covalent modification of the Arg amino acid (e.g. sidechain, peptide bond, hydrogen)? The nature of the mutation (e.g. natural or man-made) is unclear.

F. Claim 22, 23, 112 and 113 the phrase "comprises residues 741 to 794 of wild-type factor FVIII..." and "position 794 ... threonine (and leucine) lacks clear antecedent basis since claims 17 and 107 which require deletion of the B-domain which would include these amino acid residues.

G. Use of the term "comprises residues 741-794" in claims 22 and 112 which is dependent upon claims 21 and 111, respectively requiring a 54 residue spacer is confusing as to how "comprising" which is open ended further modifies the sequence 741-794 which is already restricted to 54 amino acids. In other words, what additional structure is encompassed by the use of the term "comprising" in claims 22 and 112?

H. Use of the term "residue(s)" in claims 21-23 and claims 111-113 should specify "amino acid residues" if that is what is intended. If not, the claim is indefinite as to what structure outside of an "amino acid" is encompassed.

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8. Claims 22, 23, 112 and 113 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. The phrase "comprises residues 741 to 794 of wild-type factor FVIII..." and "position 794 ... threonine (and leucine)" which include B-domain amino acid residues (up to the entire B-domain) fail to limit claims 17 and 107 that requires deletion of the B-domain. Claims 22 and 112 which recite the term "*comprises* residues 741-794" fail to further limit claims 21 and 111, respectively that require the spacer be limited to 54 residues; use of the term "comprising" is open ended and would include a spacer which is larger than 54 amino acid residues. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

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10. Claims 17, 27, 107 and 120 are rejected under 35 U.S.C. 102(b) as being anticipated by WPIDS English Abstract 88-362113 of EP 295597 (12/88). The EP reference discloses a factor 8 derivative compound and its preparation in pharmaceuticals for treating hemophilia which lacks both the B domain and the vWF binding site (e.g. lacks 741-1689: wherein the B domain is 741-1648 and the vWF binding site is 1649-1689) and which possesses a mutated Arg-740 which acts an amino acid sequence spacer which connects the A1-A2 segment to the C1-C2 segment..

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

12. Claims 17, 20-22, 27, 107, 110-112 and 120 are rejected under 35 U.S.C. 103(a) as being unpatentable over WPIDS Abstract 88-362113 of EP 295597 (12/88) and Kaufman et al., U.S. Pat. No. 5,451,521 (9/95)..

The EP reference discloses a factor 8 derivative compound and pharmaceuticals for treating hemophilia which lacks both the B domain and the vWF binding site (e.g. lacks 741-1689: wherein the B domain is 741-1648 and the vWF binding site is 1649-1689) and which possesses a mutated Arg-740 which acts an amino acid sequence spacer which connects the A1-A2 segment to the C1-C2 segment. The EP reference differs from the presently claimed invention by failing to

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recite the Arg-740 mutation (e.g. Arg to Ala) and the use of a spacer which comprises a B-domain peptide. However, the Kaufman reference discloses the making of procogulant factor VIII derivatives of formula A-X-B wherein A is 1-372 and B is 1690-2332 and X is a linking moiety which may comprise 0-1316 amino acids especially those amino acids selected from the sequence Arg-372 to Ser-1690 with a preferred embodiment incorporating Arg 372-Arg740 (e.g. see col. 8-9). Thus, Kaufman provides motivation to the skilled artisan to attach the A1-A2 heavy chain fragment to the light chain C1-C2 fragment utilizing amino acid linkers derived from the B chain of any length; of which is not critical. The Kaufman reference further teaches the replacement of Arg residues at position 740 (e.g. see Abstract) with non-conservative amino acid substitutions, including Ile, in order to obtain proteolytic resistance (e.g. see col. 2, lines 40-67 and Table II in col. 9). Accordingly, the substitution of Arg 740 with other nonconservative amino acids which possess similar side chain properties to Ile (e.g. aliphatic non-charged e.g. nonpolar), such as alanine or valine would have been obvious to one of ordinary skill in the art who wishes to obtain further proteolytic resistant derivatives. Thus, the modification of the EP reference peptide to incorporate a linking peptide which comprises B-chain residues and the further substitution of Arg with aliphatic non-charged amino acid residues (e.g. Ile, Val or Ala) would have been obvious in view of the teaching of the Kaufman reference to use such modifications in order to make procoagulant proteins.

Application/Control Number: 08/980,038

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General information regarding further correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Celsa whose telephone number is (703) 305-7556.

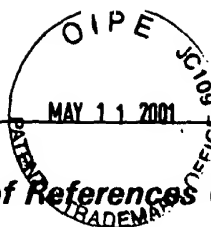
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Bennett Celsa

AS L
January 19, 1999

BENNETT CELSA
JAN 19 1999



Notice of References Cited

Application No.
08/980,038

Applicant(s)
Kaufman et al.

Examiner
Bennett Celsa

Group Art Unit
1654

Page 1 of 1

U.S. PATENT DOCUMENTS

	DOCUMENT NO.	DATE	NAME	CLASS	SUBCLASS
A					
B					
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E					
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G					
H					
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J					
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FOREIGN PATENT DOCUMENTS

	DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUBCLASS
N	0,295,597	12/88	EP	Egon et al.	----	----
O						
P						
Q						
R						
S						
T						

NON-PATENT DOCUMENTS

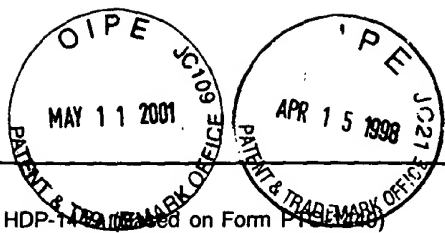
	DOCUMENT (Including Author, Title, Source, and Pertinent Pages)	DATE
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<p>FORM HD-1449 (Based on Form PTO-1449)</p> <p>PATENT AND TRADEMARK OFFICE</p> <p>INFORMATION DISCLOSURE CITATION</p> <p>(Use several sheets if necessary)</p> <p>Sheet 5 of 6</p>	<p>ATTORNEY DOCKET NO.</p> <p>2115S-001184USB</p>	<p>SERIAL NO.</p> <p>08/980,038</p>
	<p>APPLICANT</p> <p>Randal J. Kaufman et al.</p>	
	<p>FILING DATE</p> <p>November 26, 1997</p>	<p>GROUP</p> <p>1654</p>

39.		Pittman, D.D. et al., "Post-translational Requirements for Functional Factor V and Factor VIII Secretion in Mammalian Cells," <i>The Journal Of Biological Chemistry</i> 269:17329-17337 (1994)
40.		Pittman, D.D. et al., "Role of the B Domain for Factor VIII and Factor V Expression and Function," <i>Blood</i> 84:4214-4225 (1994)
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49.		Varadi, K. et al., "Influence of Factor V and Factor Va on APC-Induced Cleavage of Human Factor VIII," <i>Thrombosis and Haemostasis</i> 73:730-731 (1995)
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52.		Walker, F.J. et al., "Inactivation of Factor VIII by Activated Protein C and Protein S," <i>Archives Of Biochemistry and Biophysics</i> 252:322-328 (1987)
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Examiner: <u>B. C. LSA</u>	Date Considered: <u>11/14/99</u>
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EXAMINER: Please initial if citation considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.



FORM HDP-114 (Based on Form PTO-2000) PATENT AND TRADEMARK OFFICE INFORMATION DISCLOSURE CITATION (Use several sheets if necessary) Sheet 4 of 6	ATTORNEY DOCKET NO. 2115S-001184USB	SERIAL NO. 08/980,038
	APPLICANT Randal J. Kaufman et al.	
	FILING DATE November 26, 1997	GROUP 1654

26.		Kaufman, R.J. et al., "Synthesis, Processing, and Secretion of Recombinant Human Factor VIII Expressed in Mammalian Cells," <i>The Journal Of Biological Chemistry</i> 263:6352-6362 (1988)
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Examiner: <i>B c c c s A</i>	Date Considered: <i>11/19/97</i>
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<p>FORM HD-1449 (Based on Form PTO-1449)</p> <p>PATENT AND TRADEMARK OFFICE</p> <p>INFORMATION DISCLOSURE CITATION</p> <p>(Use several sheets if necessary)</p> <p>Sheet 3 of 6</p>	<p>ATTORNEY DOCKET No.</p> <p>2115S-001184USB</p>	<p>SERIAL No.</p> <p>08/980,038</p>
	<p>APPLICANT</p> <p>Randal J. Kaufman et al.</p>	
	<p>FILING DATE</p> <p>November 26, 1997</p>	<p>GROUP</p> <p>1654</p>

12.	<i>ML</i>	Eaton, D. et al., "Proteolytic Processing of Human Factor VIII. Correlation of Specific Cleavages by Thrombin, Factor Xa, and Activated Protein C with Activation and Inactivation of Factor VIII Coagulant Activity," <i>Biochemistry</i> 25:505-512 (1986)
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Examiner: <i>B. C. C. S. A.</i>	Date Considered: <i>1/19/99</i>
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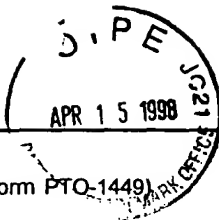


FORM HDP-1449 (Based on Form PTO-1449) PATENT AND TRADEMARK OFFICE INFORMATION DISCLOSURE CITATION (Use several sheets if necessary) Sheet 2 of 6	ATTORNEY DOCKET NO. 2115S-001184USB	SERIAL NO. 08/980,038
	APPLICANT Randal J. Kaufman et al.	
	FILING DATE November 26, 1997	GROUP 1654

OTHER DOCUMENTS (Including Author, Title, Date, Pertinent Pages, etc.)		
Ref. Desig.	Examiner's Initials	
1.		Blond-Elguindi, S. et al., "Affinity Panning Of A Library Of Peptides Displayed On Bacteriophages Reveals The Binding Specificity Of BIP," <i>Cell</i> 75:717-728 (1993)
2.		Bertina, R.M. et al., "Mutation in blood coagulation factor V associated with resistance to activated protein C," <i>Nature</i> 369:64-67 (1994)
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Examiner: <u>B. C. K. S. A</u>	Date Considered: <u>11/19/99</u>
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FORM HDP-1449 (Based on Form PTO-1449) PATENT AND TRADEMARK OFFICE INFORMATION DISCLOSURE CITATION (Use several sheets if necessary) Sheet 1 of 6	ATTORNEY DOCKET No.	SERIAL No.
	2115S-001184USB	08/980,038
	APPLICANT Randal J. Kaufman et al.	
	FILING DATE	GROUP
	November 26, 1997	1654

U.S. PATENT DOCUMENTS						
Ref. Desig.	Examiner's Initials	Document Number	Date	Name	Class/ Subclass	(If appropriate) Filing Date
1.	ML	4,757,006	7/1988	Toole, Jr. et al.	435/68	ML -
2.	ML	5,250,421	10/1993	Kaufman et al.	435/69.6	—
3.	ML	5,563,045	10/1996	Pittman et al.	435/69.6	—
4.	ML	4,868,112	9/1989	Toole, Jr.	435/68	ML -
5.	ML	5,004,803	4/1991	Kaufman et al.	530/383	383 -
6.	ML	5,045,455	9/1991	Kuo et al.	435/69.6	—
7.	ML	5,214,033	5/1993	Zimmerman et al.	514/21	—
8.	ML	5,451,521	9/1995	Kaufman et al.	435/240.2	—

FOREIGN PATENT DOCUMENTS							
Ref. Desig.	Examiner's Initials	Document Number	Date	Country	Class/ Subclass	Translation	
						Yes	No
1.	ML	WO 87/07144	12/1987	PCT International	7		
2.		WO 87/04187	7/1987	PCT International			
3.		WO 88/08035	10/1988	PCT International			
4.		WO 88/03558	5/1988	PCT International			
5.		WO 87/06101	10/1987	PCT International			
6.		WO 91/07490	5/1991	PCT International			
7.		WO 97/03194	1/1997	PCT International			
8.		WO 97/03195	1/1997	PCT International			
9.	ML	0 197 901 B1	7/1991	Europe			

Examiner: B CULSA	Date Considered: 11/19/99
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FORM HDP-1449 (Based on Form PTO-1449) PATENT AND TRADEMARK OFFICE INFORMATION DISCLOSURE CITATION (Use several sheets if necessary) Sheet 1 of 1	ATTORNEY DOCKET No.	SERIAL No.
	2115S-001184USB	08/980,038
	APPLICANT Randal J. Kaufman et al.	
	FILING DATE	GROUP
	November 26, 1997	1654

U.S. PATENT DOCUMENTS						
Ref. Desig.	Examiner's Initials	Document Number	Date	Name	Class/ Subclass	(If appropriate) Filing Date
1.	CL	5,661,008	8/1997	Almstedt et al.	435/69.6	12/92

FOREIGN PATENT DOCUMENTS							
Ref. Desig.	Examiner's Initials	Document Number	Date	Country	Class/ Subclass	Translation	
						Yes	No

OTHER DOCUMENTS (including Author, Title, Date, Pertinent Pages, etc.)		
Ref. Desig.	Examiner's Initials	

Examiner: B CLSA	Date Considered: 1/19/99
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FORM HDP-1449 (Based on Form PTO-1449) PATENT AND TRADEMARK OFFICE INFORMATION DISCLOSURE CITATION (Use several sheets if necessary) Sheet 6 of 6	ATTORNEY DOCKET NO. 2115S-001184USB	SERIAL NO. 08/980,038
	APPLICANT Randal J. Kaufman et al.	
	FILING DATE November 26, 1997	GROUP 1654

54.		Wood, W.I. et al., "Expression of active human factor VIII from recombinant DNA clones," <i>Nature</i> 312:330-337 (1984)
55.		Shima, M. et al., "Common Inhibitory Effects Of Human Anti-2 Domain Inhibitor Alloantibodies On Factor VIII Binding To Von Willebrand," <i>Blood</i> Vol. 86, Abstract No. 748 (1995)
56.		Beyte, A. et al., "Sulfation of Tyr ¹⁶⁸⁰ of Human Blood Coagulation Factor VIII Is Essential for the Interaction of Factor VIII with von Willebrand Factor, <i>The Journal of Biological Chemistry</i> 266:740-746 (1991)
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58.		Pipe, S.W. et al., "Characterization of a genetically engineered inactivation-resistant coagulation factor VIIIa," <i>PNAS (USA)</i> 94:11851-11856 (1997)
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Examiner: B. C. C. S. A	Date Considered: 11/19/99
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FILING DATE	October 17, 1997	GROUP
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JAN 26 1998

EXAMINER INITIAL	DOCUMENT NUMBER	DATE	NAME	CLASS	SUB CLASS	FILING DATE IF APPROPRIATE
	3,489,148	1/13/70	Duncan, et al.			
	3,814,101	6/4/74	Kozak			
	3,860,003	1/14/75	Buell			
	3,896,807	7/29/75	Buchalter			
	4,589,876 B1	4/27/93	Van Tilburg			
	4,623,339	11/18/86	Ciraldi, et al.			
	4,636,207 B1	11/14/89	Buell			
	4,695,278	9/22/87	Lawson			
	4,795,454	1/3/89	Dragoo			
	4,834,737	5/30/89	Khan			
	5,026,364	6/25/91	Robertson			
	5,151,092	9/29/92	Buell, et al.			
	5,525,346	6/11/96	Hartung, et al.			
	5,569,230	10/29/96	Roe, et al.			
	5,569,232	10/29/96	Buell, et al.			
	5,569,234	10/29/96	Buell, et al.			
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	5,580,411	12/3/96	Nease, et al.			
	5,582,605	12/10/96	Lepie			
	5,607,760	3/4/97	Roe			
	5,609,587	3/11/97	Roe			
	5,624,676	4/29/97	Mackey, et al.			
	5,635,191	6/3/97	Roe, et al.			
	5,643,588	7/1/97	Roe, et al.			
	5,649,917	7/22/97	Roberts, et al.			
	5,656,591	8/12/97	Tomita, et al.			

		DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUB CLASS	TRANSLATION YES NO

EXAMINER	DATE CONSIDERED
EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609; draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.	



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SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
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EXAMINER

ART UNIT	PAPER NUMBER
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DATE MAILED:

EXAMINER INTERVIEW SUMMARY RECORD

All participants (applicant, applicant's representative, PTO personnel):

(1) SENNETT CELSA (3) _____
(2) DEANN E SMITH (301633) (4) _____

Date of interview 11/12/02

Type: ☐ Telephonic ☒ Personal (copy is given to ☐ applicant ☐ applicant's representative).

Exhibit shown or demonstration conducted: ☐ Yes ☒ No. If yes, brief description: _____

Agreement ☐ was reached with respect to some or all of the claims in question. ☒ was not reached.

Claims discussed: claims of record

Identification of prior art discussed: NONE

Description of the general nature of what was agreed to if an agreement was reached, or any other comments: Applicant's representative discussed the restriction requirement in view of the remaining and added claims and argued for rejoinder of the selected sp with some other gps.

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

☐ 1. It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph below has been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW (e.g., items 1-7 on the reverse side of this form). If a response to the last Office action has already been filed, then applicant is given one month from this interview date to provide a statement of the substance of the interview.

☐ 2. Since the examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the substance of the interview unless box 1 above is also checked.

[Signature]
Examiner's Signature

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SERIAL NUMBER	FILING DATE	FIRST	NAMED APPLICANT	ATTORNEY DOCKET NO.
08/ 940,038				

EXAMINER	
ART UNIT	PAPER NUMBER

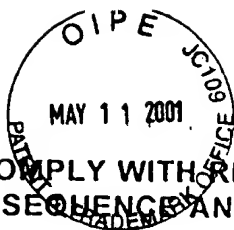
DATE MAILED:

Please find below a communication from the EXAMINER in charge of this application

Commissioner of Patents

1. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.
2. Any inquiry concerning this communication should be directed to Examiner Celsa, Art Unit ~~1011~~ ¹⁶⁵⁴, whose telephone number is (703)305-7556.
3. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.
4. Any questions regarding compliance with the sequence rules requirements specifically should be directed to the departments listed at the bottom of the Notice to Comply.
5. APPLICANT IS GIVEN ONE MONTH FROM THE DATE OF THIS LETTER WITHIN WHICH TO COMPLY WITH THE SEQUENCE RULES, 37 C.F.R. §§ 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 C.F.R. § 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 C.F.R. § 1.136. In no case may an applicant extend the period for response beyond the six month statutory period. Direct the response to the undersigned. Applicant is requested to return a copy of the attached Notice to Comply with the response.

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Application No. 08/980,038

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 CFR 1.821 - 1.825 for the following reason(s):

- ☒ 1. This application clearly fails to comply with the requirements of 37 CFR 1.821 - 1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.
- ☒ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 CFR 1.821(c).
- ☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 CFR 1.821(e).
- ☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 CFR 1.822 and/or 1.823, as indicated on the attached marked-up copy of the "Raw Sequence Listing."
- ☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A substitute computer readable form must be submitted as required by 37 CFR 1.825(d).
- ☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 CFR 1.821(e).
- ☐ 7. Other: _____

Applicant must provide:

- ☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing"
- ☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification
- ☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d)

For questions regarding compliance with these requirements, please contact:

For Rules Interpretation, call (703) 308-1123
For CRF submission help, call (703) 308-4212
For PatentIn software help, call (703) 308-6856

Please return a copy of this notice with your response.



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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/980,038	11/26/97	KAUFMAN	R 2115001184US

OMV-118401

EXAMINER

CELSA, B

ART UNIT	PAPER NUMBER
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1627

24

DATE MAILED: 10/11/00

DE ANN F. SMITH
LAHIVE & COCKFIELD, LLP
28 STATE STREET
BOSTON MA 02109

HM12/1011

DOCKETED

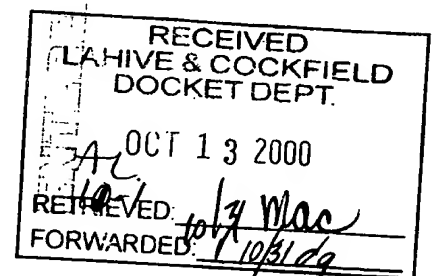
Dec 14, 2000 - AMENDMENT AFTER FINAL (Exp Pro)

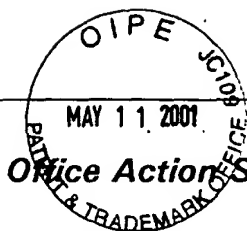
Jan 8, 2001 - AMENDMENT AFTER FINAL/APPEAL W/O FEES

April 11, 2001 - ESP/FINAL REJECTION
FILE APPEAL OR CONTINUATION

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks





Office Action Summary	Application No. 08/980,038	Applicant(s) Kaufman et al.
	Examiner Bennett Celsa	Group Art Unit 1627

☒ Responsive to communication(s) filed on Jul 20, 2000

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 17-23, 27, 32, 36, and 102-147 is/are pending in the application.

Of the above, claim(s) 18, 19, 32, 36, 102-106, 108, 109, 114-119, and 123 are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 17, 20-23, 27, 107, 110-113, 120, 146, and 147 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
☐ received.

☐ received in Application No. (Series Code/Serial Number) _____

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

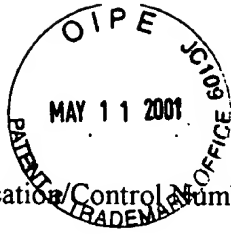
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☒ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---



Application/Control Number: 08/980,038

Page 2

Art Unit: 1627

DETAILED ACTION

Continued Prosecution Application

1. The request filed on 7/20/00 in paper no. 23 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 08/980,038 is acceptable and a CPA has been established. An action on the CPA follows.
2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

Claims 17-23, 27, 32, 36 and 102-147 are currently pending (claims 146 and 147 are newly added).

Claims 18-19, 32, 36, 102-106, 108-109, 114-119 and 121-145 are withdrawn from consideration as being directed to a nonelected invention.

Claims 17, 20-23, 27, 107, 110-113, 120, 146 and 147 are under consideration.

Outstanding Objection(s) and Rejection(s)

3. Claims 17, 20-23, 27, 107, 110-113, 120, 146 and 147 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In claims 17 and 107, the structure of the human factor FVIII polypeptide which is modified to attain the "procoagulant-active FVIII protein) is indefinite. One needs to know the starting point (e.g. the initial polypeptide structure) in order to determine a final product which would infringe or not infringe the claim. Thus, the metes and bounds of the final protein are not known if the metes and bounds of the starting polypeptide are not described.

Art Unit: 1627

- B. In claims 17 and 107, the term "the B domain" lacks antecedent basis.
- C. In claims 17 and 107, the term "the von Willebrand factor binding site" lacks antecedent basis.
- D. In claims 17 and 107, the term "the A2- and A3- domains" lack antecedent basis.
- E. In claims 17 and 107, the phrase "a mutation at Arg740" lacks metes and bound as to what the metes and bounds of such mutations are. Do mutations include a deletion of Arg740 ? Only substitutions of Arg740 ? A covalent modification of the Arg amino acid (e.g. sidechain, peptide bond, hydrogen)? The nature of the mutation (e.g. natural or man-made) is unclear.
- F. Claim 22, 23, 112, 113, 146 and 147 the phrase "comprises residues 741 to 794 of wild-type factor FVIII..." and "position 794 ... threonine (and leucine) lacks clear antecedent basis since claims 17 and 107 which require deletion of the B-domain which would include these amino acid residues. Additionally, with respect to new claims 146 and 147, "comprising" would encompass the entire B-domain which is contradictory to the claimed absence of the B-domain.
4. Claims 146 and 147 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. The phrase "comprises residues 741 to 794 of wild-type factor FVIII..." and "position 794 ... threonine (and leucine)" which include B-domain amino acid residues (up to the entire B-domain) fail to limit claims 17 and 107 that requires deletion of the B-domain. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.
5. Claims 17, 27, 107 and 120 are rejected under 35 U.S.C. 102(b) as being anticipated by WPIDS English Abstract 88-362113 or EP 295597 (12/88) (which is attached for applicant's convenience).

The EP reference discloses a factor 8 derivative compound and its preparation in pharmaceuticals for treating hemophilia which lacks both the B domain and the vWF binding site (e.g. lacks 741-1689: wherein the B domain is 741-1648 and the vWF binding site is 1649-1689) and which possesses a mutated Arg-740 which acts an amino acid sequence spacer which connects the A1-A2 segment to the C1-C2 segment. The reference further discloses that "the new protein possesses a rapid activation by thrombin aside from a procoagulation activity that is very similar to one of the authentic protein and biologic half-value time" (e.g. see translation at page 2, lines 9-12). Thus the reference protein is stable and possesses a good specific activity. Accordingly, the reference meets the critical chemical claim limitations (e.g. absence of a B domain and Vwf binding site; and presence of a linking amino acid) and possesses improved

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properties and thus would be expected to "inherently" possess the same conformational structure upon thrombin activation as presently claimed. See MPEP 2112.02 and *In re Spada*, 15 USPQ2d 1655,1658 (Fed. Cir. 1990)("Products of identical chemical composition can not have mutually exclusive properties"). The Examiner lacks the facilities to test the reference protein to see if it meets functional limitations; thus placing the burden directly on applicant (e.g. See *In re Brown*, 173 USPQ 685,688 (CCPA 1972)).

6. Claims 17, 20-22, 27, 107, 110-112, 120, 146 and 147 are rejected under 35 U.S.C. 103(a) as being unpatentable over WPIDS Abstract 88-362113 of EP 295597 (or translation thereof) (12/88) and Kaufman et al., U.S. Pat. No. 5,451,521 (9/95)..

The EP reference discloses a factor 8 derivative compound and pharmaceuticals for treating hemophilia which lacks both the B domain and the vWF binding site (e.g. lacks 741-1689; wherein the B domain is 741-1648 and the vWF binding site is 1649-1689) and which possesses a mutated Arg-740 which acts an amino acid sequence spacer which connects the A1-A2 segment to the C1-C2 segment. The EP reference differs from the presently claimed invention by failing to recite the Arg-740 mutation (e.g. Arg to Ala) and the use of a spacer which comprises a B-domain peptide.

However, the Kaufman reference discloses the making of procogulant factor VIII derivatives of formula A-X-B wherein A is 1-372 and B is 1690-2332 and X is a linking moiety which may comprise 0-1316 amino acids especially those amino acids selected from the sequence Arg-372 to Ser-1690 with a preferred embodiment incorporating Arg 372-Arg740 (e.g. see col. 8-9). Thus, Kaufman provides motivation to the skilled artisan to attach the A1-A2 heavy chain fragment to the light chain C1-C2 fragment utilizing amino acid linkers derived from the B chain of any length; of which is not critical. The Kaufman reference further teaches the replacement of Arg residues at position 740 (e.g. see Abstract) with non-conservative amino acid substitutions, including Ile, in order to obtain proteolytic resistance (e.g. see col. 2, lines 40-67 and Table II in col. 9). Accordingly, the substitution of Arg 740 with other nonconservative amino acids which possess similar side chain properties to Ile (e.g. aliphatic non-charged e.g. nonpolar), such as alanine or valine would have been obvious to one of ordinary skill in the art who wishes to obtain further proteolytic resistant derivatives. Thus, the modification of the EP reference peptide to incorporate a linking peptide which comprises B-chain residues and the further substitution of Arg with aliphatic non-charged amino acid residues (e.g. Ile, Val or Ala) would have been obvious in view of the teaching of the Kaufman reference to use such modifications in order to make procoagulant proteins.

Accordingly, the EP reference combined with the Kaufman reference render obvious proteins within the scope of the presently claimed invention. Accordingly, the above reference(s)

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meet the critical chemical claim limitations (e.g. absence of a B domain and Vwf binding site; and presence of a linking amino acid) and possesses improved properties and thus would be expected to possess the same conformational structure upon thrombin activation as presently claimed. See MPEP 2112.02 and *In re Spada*, 15 USPQ2d 1655,1658 (Fed. Cir. 1990) ("Products of identical chemical composition can not have mutually exclusive properties"). The Examiner lacks the facilities to test reference protein (s) to see if it meets functional limitations; thus placing the burden directly on applicant (e.g. See *In re Brown*, 173 USPQ 685,688 (CCPA 1972)).

7. Claims 17 and 107 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (e.g. New Matter Rejection).

Applicant's newly added functional/conformational limitation is clearly broader than that described on page 9, line 6-11 which is limited to thrombin activation, with the further description of the covalent association of the A2 domain with the light chain..

8. This is a CPA of applicant's earlier Application No. 08/980,038. All claims are drawn to the same invention claimed in the earlier application and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the earlier application. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action in this case. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no, however, event will the statutory period for reply expire later than **SIX MONTHS** from the mailing date of this final action.

Application/Control Number: 08/980,038

Page 6

Art Unit: 1627

General information regarding further correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Celsa whose telephone number is (703) 305-7556.


If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat (art unit 1627), can be reached at (703)308-0570.

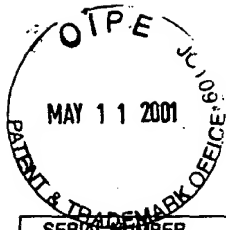
Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Bennett Celsa (art unit 1627)

October 2, 2000

**BENNETT CELSA
PRIMARY EXAMINER**





UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
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62/450,038

EXAMINER

ART UNIT	PAPER NUMBER
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20

DATE MAILED:

EXAMINER INTERVIEW SUMMARY RECORD

All participants (applicant, applicant's representative, PTO personnel):

(1) De ANN F. Smith (3) _____

(2) Bennett Celsa (4) _____

Date of Interview 11/5/97

Type: ☒ Telephonic ☐ Personal (copy is given to ☐ applicant ☐ applicant's representative).

Exhibit shown or demonstration conducted: ☐ Yes ☒ No. If yes, brief description: _____

Agreement ☐ was reached with respect to some or all of the claims in question. ☒ was not reached.

Claims discussed: of record

Identification of prior art discussed: of record

Description of the general nature of what was agreed to if an agreement was reached, or any other comments: Agreement will

provide a response to outstanding office action

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

☒ 1. It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph below has been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW (e.g., items 1-7 on the reverse side of this form). If a response to the last Office action has already been filed, then applicant is given one month from this interview date to provide a statement of the substance of the interview.

☐ 2. Since the examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the substance of the interview unless box 1 above is also checked.



Office No. UMV-1184CPCPA

THE "RECEIVED" STAMP OF THE PATENT AND TRADEMARK OFFICE
IMPRINTED HEREON ACKNOWLEDGES THE FILING OF:

Description of Paper* and No.: Transmittal Letter (in duplicate); Continued Prosecution Application Request Transmittal (in duplicate); Request for Five-Month Extension of Time; Checks in the amount of \$345.00(appln fee) and \$925.00 (extension fee); and this acknowledgment postcard.

Name of Applicant(s): Randal J. Kaufman, et al.

Intf. or Serial No.: CPA of Serial No.: 08/980,038

Atty: DeAnn F. Smith/acl

Date: July 20, 2000

*with Certificate of Express Mailing No. EL 373212392 US



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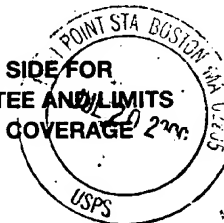


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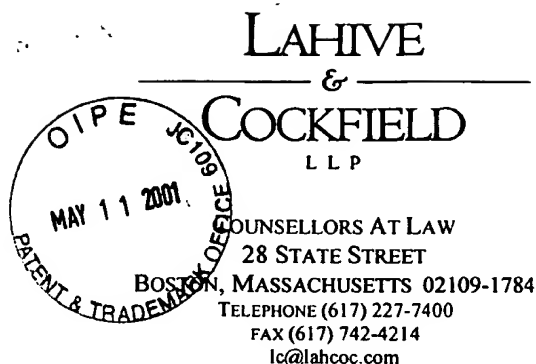
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DeANN FORAN SMITH**

* Admitted in NY only
** Admitted in MI only
*** Passed the Patent Bar Examination

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July 20, 2000

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Assistant Commissioner for Patents
Washington, D.C. 20231

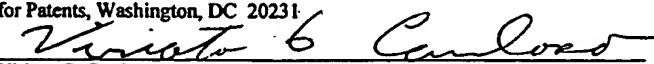

Re: U.S. Patent Application Serial No. 08/980,038 (CPA filed herewith)
Applicants: Randal J. Kaufman, et al.
Title: *INACTIVATION RESISTANT FACTOR VIII*
Filed: November 26, 1997
Examiner: Celsa, B., Group Art Unit: 1654
Attorney Docket No.: UMV-1184CPCPA

Dear Sir:

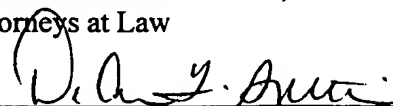
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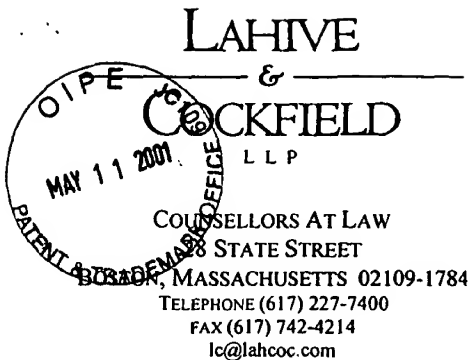
1. Continued Prosecution Application (CPA) Request Transmittal (in duplicate);
2. Request for Five-Month Extension of Time;
3. Checks in the amount of \$345.00 (appln fee) and \$925.00(extension fee); and
4. A return postcard.

Please charge any deficiencies in late fees to our Deposit Account No. 12-0080. The undersigned requests any extensions of time necessary to respond. A duplicate of this sheet is enclosed.

"Express Mail" mailing label number	EL 373212392 US
Date of Deposit	July 20, 2000
I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to BOX CPA, Assistant Commissioner for Patents, Washington, DC 20231.	
	
Viriato G. Cardoso	
	
Please Print Name of Person Signing	

LAHIVE & COCKFIELD, LLP
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By 
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Facsimile - 617-742-4214



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July 20, 2000

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Assistant Commissioner for Patents
Washington, D.C. 20231

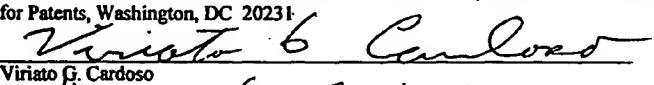

Re: U.S. Patent Application Serial No. 08/980,038 (CPA filed herewith)
Applicants: Randal J. Kaufman, et al.
Title: *INACTIVATION RESISTANT FACTOR VIII*
Filed: November 26, 1997
Examiner: Celsa, B., Group Art Unit: 1654
Attorney Docket No.: UMV-1184CPCPA

Dear Sir:

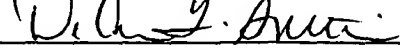
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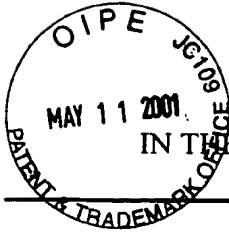
1. Continued Prosecution Application (CPA) Request Transmittal (in duplicate);
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3. Checks in the amount of \$345.00 (appln fee) and \$925.00(extension fee); and
4. A return postcard.

Please charge any deficiencies in late fees to our Deposit Account No. 12-0080. The undersigned requests any extensions of time necessary to respond. A duplicate of this sheet is enclosed.

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Date of Deposit	July 20, 2000
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Viriato G. Cardoso	
	
Please Print Name of Person Signing	

LAHIVE & COCKFIELD, LLP
Attorneys at Law

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DeAnn F. Smith, Esq.
Registration No. 36,683
28 State Street
Boston, MA 02109
Telephone - 617-227-7400
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Randal J. Kaufman, et al.

Group Art Unit: 1654

Serial No.: 08/980,038

Examiner: Celsa, B.

Filed: November 26, 1997

For: *INACTIVATION RESISTANT FACTOR VIII*

Attorney Docket No.: UMV-1184CPCPA

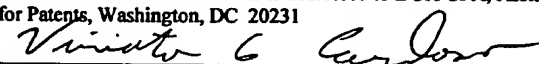
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Washington, D.C. 20231

REQUEST FOR FIVE-MONTH EXTENSION OF TIME

Dear Sir:

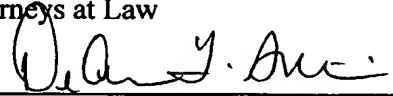
Appellants request an extension of time for filing the Appeal Brief for five months from February 21, 2000 to July 21, 2000. In lieu of an Appeal Brief, a Continued Prosecution Application (CPA) is being filed concurrently. Enclosed is a check which covers the appropriate fee of \$925.00 based on small entity status.

Please charge any underpayments or credit any overpayments to our Deposit Account No. 12-0080. A duplicate of this sheet is enclosed.

"Express Mail" mailing label number	EL 373212392 US
Date of Deposit	July 20, 2000
I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to BOX CPA, Assistant Commissioner for Patents, Washington, DC 20231	
	
Viriato G. Cardoso	
Please Print Name of Person Signing	

Dated: July 20, 2000

LAHIVE & COCKFIELD, LLP
Attorneys at Law

By 
DeAnn F. Smith, Esq.
Registration No. 36,683
28 State Street
Boston, MA 02109
Telephone - 617-227-7400
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Randal J. Kaufman, et al.

Group Art Unit: 1654

Serial No.: 08/980,038

Examiner: Celsa, B.

Filed: November 26, 1997

For: *INACTIVATION RESISTANT FACTOR VIII*

Attorney Docket No.: UMV-1184CPCPA

BOX CPA
Assistant Commissioner for Patents
Washington, D.C. 20231

REQUEST FOR FIVE-MONTH EXTENSION OF TIME

Dear Sir:

Appellants request an extension of time for filing the Appeal Brief for five months from February 21, 2000 to July 21, 2000. In lieu of an Appeal Brief, a Continued Prosecution Application (CPA) is being filed concurrently. Enclosed is a check which covers the appropriate fee of \$925.00 based on small entity status.

Please charge any underpayments or credit any overpayments to our Deposit Account No. 12-0080. A duplicate of this sheet is enclosed.

"Express Mail" mailing label number EL 373212392 US
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Viriato G. Cardoso
Viriato G. Cardoso
Viriato G. Cardoso
Please Print Name of Person Signing

LAHIVE & COCKFIELD, LLP
Attorneys at Law

By DeAnn F. Smith
DeAnn F. Smith, Esq.
Registration No. 36,683
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Boston, MA 02109
Telephone - 617-227-7400
Facsimile - 617-742-4214

Dated: July 20, 2000



Office No. UMV-1184CP

**THE "RECEIVED" STAMP OF THE PATENT AND TRADEMARK OFFICE
IMPRINTED HEREON ACKNOWLEDGES THE FILING OF:**

Description of Paper* and No.: Transmittal Letter; Notice of Appeal from the Primary Examiner to the Board of Patent Appeals and Interferences (in duplicate); Request for Three-Month Extension of Time (in duplicate); Checks in the amount of \$150.00 (appeal fee) and \$435 (extension); and this return receipt postcard.

Title: *INACTIVATION RESISTANT FACTOR VIII*

Name of Applicant(s): Randal J. Kaufman et al.

Intf. or Serial No.: 08/980,038

Atty: DeAnn F. Smith, Esq.

Date: December 21, 1999

*with Certificate of First Class Mailing





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ERICK B. BERGLUND, Ph.D.

December 21, 1999

Assistant Commissioner for Patents
Box AF
Washington, D.C. 20231

Re: U.S. Serial No. 08/980,038 – Filed November 26, 1997
Title: INACTIVATION RESISTANT FACTOR VIII
Applicants: Randal J. Kaufman et al.
Attorney Docket No.: UMV-1184CP

Dear Sir:

I enclose herewith for filing in the above-identified application the following:

1. Notice From The Primary Examiner To The Board Of Patent Appeals And Interferences;
2. Request for Three-Month Extension of Time; and
3. Checks for \$150.00 (appeal) and \$435.00 (extension).

Please charge any necessary fees to our Deposit Account No. 12-0080. The undersigned requests any extensions of time necessary to respond.

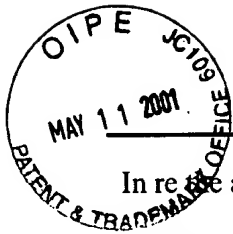
<p>Certificate of First Class Mailing (37 CFR 1.8(a))</p> <p>I hereby certify that this correspondence is deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Box AF, Washington, DC 20231 on:</p> <p>December 21, 1999 Date</p> <p><i>DeAnn F. Smith</i> DeAnn F. Smith, Esq., Reg. No. 36,683</p>

Respectfully submitted,

LAHIVE & COCKFIELD, LLP

DeAnn F. Smith

DeAnn F. Smith, Esq.
Reg. No. 36,683



BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In re the application of: Randal J. Kaufman *et al.*

Serial No.: 08/980,038

Filed: November 26, 1997

For: INACTIVATION RESISTANT FACTOR VIII

Attorney Docket No.: UMV-1184CP

Group Art Unit: 1654

Examiner: B. Celsa

Assistant Commissioner for Patents
Box AF
Washington, D.C. 20231

**NOTICE OF APPEAL FROM THE PRIMARY EXAMINER TO
THE BOARD OF PATENT APPEALS AND INTERFERENCES**

Dear Sir:

Applicant hereby appeals to the Board of Patent Appeals and Interferences from the decision dated June 30, 1999 of the Primary Examiner finally rejecting claims 17, 20-23, 27, 107, 110-113, 120, 146 and 147.

The Appeal Fee of \$150.00 for small entity is enclosed. If for any reason the fee is insufficient, please charge the balance to Deposit Account 12-0080 of the undersigned attorneys.

A duplicate of this sheet is enclosed.

<p><u>Certificate of First Class Mailing (37 CFR 1.8(a))</u></p> <p>I hereby certify that this correspondence is deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Box AF, Washington, DC 20231 on:</p> <p>December 21, 1999 Date</p> <p><i>DeAnn F. Smith</i> DeAnn F. Smith, Esq., Reg. No. 36,683</p>
--

Respectfully submitted,

DeAnn F. Smith

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Randal J. Kaufman *et al.*

Serial No.: 08/980,038

Filed: November 26, 1997

For: INACTIVATION RESISTANT FACTOR VIII

Attorney Docket No.: UMV-1184CP

Group Art Unit: 1654

Examiner: B. Celsa

Assistant Commissioner for Patents
Box AF
Washington, D.C. 20231

REQUEST FOR THREE-MONTH EXTENSION OF TIME

Dear Sir:

Applicants request a three-month extension of time pursuant to 37 CFR 1.136(a) in which to respond to the outstanding Office Action dated June 30, 1999. In lieu of a response, a Notice of Appeal is being filed concurrently herewith.

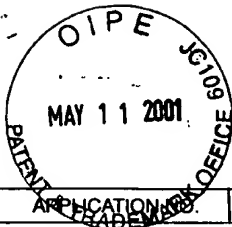
Enclosed is a check which covers the appropriate fee of \$435.00 based on small entity status. Please charge any underpayments or credit any overpayments to our Deposit Account No. 12-0080. A duplicate of this sheet is enclosed.

<p><u>Certificate of First Class Mailing (37 CFR 1.8(a))</u></p> <p>I hereby certify that this correspondence is deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Box AF, Washington, DC 20231 on:</p> <p>December 21, 1999 Date</p> <p><i>DeAnn F. Smith</i> DeAnn F. Smith, Esq., Reg. No. 36,683</p>
--

Respectfully submitted,

DeAnn F. Smith
DeAnn F. Smith, Esq.
Reg. No. 36,683
LAHIVE & COCKFIELD, LLP
28 State Street
Boston, MA 02109
(617) 227-7400

Dated: December 21, 1999



U.S. 1184 CP
**UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office**

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231 *HC*

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/980,038	11/26/97	KAUFMAN	R 2115001184US

HARNES DICKY & PIERCE
ATTORNEYS AND COUNSELLORS
PO BOX 828
BLOOMFIELD HILLS MI 48303

HM12/0630

EXAMINER

CELSA, B

ART UNIT	PAPER NUMBER
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1654

19

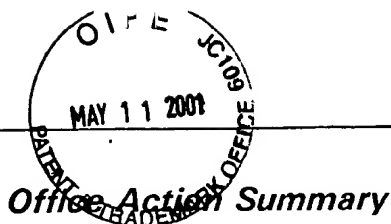
DATE MAILED:

06/30/99

DOCKETED
July 30, 1999 - 2 mo. Expedited Procedure
Sep. 30, 1999 - Final Report / Appeal / Con
Dec. 30, 1999 - ESP

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks



Office Action Summary	Application No. 08/980,038	Applicant(s) Kaufman et al.
	Examiner Bennett Celsa	Group Art Unit 1654

☒ Responsive to communication(s) filed on Apr 21, 1999

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire three month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 17-23, 27, 32, 36, and 102-147 is/are pending in the application.

Of the above, claim(s) 18, 19, 32, 36, 102-106, 108, 109, 114-119, and 12 are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 17, 20-23, 27, 107, 110-113, 120, 146, and 147 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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Response to Amendment

Applicant's amendment dated 4/21/99 is acknowledged.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Status of the Claims

Claims 17-23, 27, 32, 36 and 102-147 are currently pending (claims 146 and 147 are newly added)..

Claims 18-19, 32, 36, 102-106, 108-109, 114-119 and 121-145 are withdrawn from consideration as being directed to a nonelected invention.

Claims 17, 20-23, 27, 107, 110-113, 120, 146 and 147 are under consideration.

Sequence Rule Compliance

Applicant's Sequence listing submitted on 2/4/99 has been received and entered.

Withdrawn Objection(s) and Rejection(s)

The indefinite rejection in items G. and H. of the prior office action have been overcome by applicant's amendment.

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Outstanding Objection(s) and Rejection(s)

2. Claims 17, 20-23, 27, 107, 110-113, 120, 146 and 147 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In claims 17 and 107, the structure of the human factor FVIII polypeptide which is modified to attain the "procoagulant-active FVIII protein) is indefinite. One needs to know the starting point (e.g. the initial polypeptide structure) in order to determine a final product which would infringe or not infringe the claim. Thus, the metes and bounds of the final protein are not known if the metes and bounds of the starting polypeptide are not described.

B. In claims 17 and 107, the term "the B domain" lacks antecedent basis.

C. In claims 17 and 107, the term "the von Willebrand factor binding site" lacks antecedent basis.

D. In claims 17 and 107, the term "the A2- and A3- domains" lack antecedent basis.

E. In claims 17 and 107, the phrase "a mutation at Arg740" lacks metes and bound as to what the metes and bounds of such mutations are. Do mutations include a deletion of Arg740 ? Only substitutions of Arg740 ? A covalent modification of the Arg amino acid (e.g. sidechain, peptide bond, hydrogen)? The nature of the mutation (e.g. natural or man-made) is unclear.

F. Claim 22, 23, 112, 113, 146 and 147 the phrase "comprises residues 741 to 794 of wild-type factor FVIII..." and "position 794 ... threonine (and leucine) lacks clear antecedent basis since claims 17 and 107 which require deletion of the B-domain which would include these amino acid residues. Additionally, with respect to new claims 146 and 147, "comprising" would encompass the entire B-domain which is contradictory to the claimed absence of the B-domain.

Discussion

Applicant's arguments directed to the above indefinite rejections were considered but deemed nonpersuasive for the following reasons.

In response to item a. above applicant argues that the term "procoagulant-active FVIII protein" is clear citing prior issued patents in support and the specification disclosure of DNA

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sequences encoding human FVIII protein. However, the Examiner is confused with the starting structure that is used to derive the “procoagulant-active FVIII protein”. This is confusing to the Examiner since the claim recites “a human Factor VIII polypeptide that is modified” which implies that there is multiple human factor VIII polypeptides which may be the human form or some other modification thereof. Simply amending to delete “a” would clarify the scope of the claim to be consistent with applicant’s argument and the disclosure.

With respect to items B)-D) above, applicant argues that human factor VIII protein is well known in the art. Applicant’s argument will have merit upon clarification of the above item a. issue. Until then the above rejections for improper antecedent basis are retained, since the starting material (e.g. a human Factor VIII polypeptide that is modified) is still indefinite and thus incapable of providing proper antecedent basis. Additionally, it is noted that chemical structure which is necessary for claim interpretation (e.g. the various regions of human factor VIII) should be in the claim, since the Examiner cannot read critical claim limitations into the claim and applicant is under a duty to provide a clear indication as to what chemical structure will or will not infringe the presently claimed invention.

With respect to item E) above applicant argues that the term “mutation” refers to any alteration including but not limited to, substitutions, insertions and deletions citing the specification on page 10, lines 25-26 and Example 3 showing a single Arg740 mutation. However, the specification definition is clearly open ended (e.g. “including but not limited to”) and thus is not strictly limited to “substitutions, insertions and deletions”. Additionally, there is no

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recitations as what chemical entity or entities are substitutable or insertable at the Arg740 position nor are the possible substituents limited in length, conformation, chemical properties or any other parameter. The demonstration of a single amino acid substitution (e.g. Example 3) does not serve to limit the metes and bounds of the presently claimed invention. Additionally, it is further unclear as to how such a mutation occurs.

With respect to item F. above applicant argues that the claimed human FVIII although B-domainless can nevertheless contain a portion of the B-domain which is called a linker. Applicant's argument is misguided. For use of the term "comprising" in new claims 146 and 147 would encompass the entire B-domain, forcing applicant to argue that the claim encompasses a protein which is both B-domainless but yet also contains a B-domain. The claimed language is clearly confusing since it requires the absence of the B-domain, yet applicant's depended claim encompasses the partial to total presence of such a domain regardless of how it is labeled (e.g. as a linker or otherwise).

With respect to item G. above it is noted that this rejection, although no longer applicable to claims

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3. Claims 146 and 147 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. The phrase "comprises residues 741 to 794 of wild-type factor FVIII..." and "position 794 ... threonine (and leucine)" which include B-domain amino acid residues (up to the entire B-domain) fail to limit claims 17 and 107 that requires deletion of the B-domain. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Discussion

Applicant's argument and amendment were considered with regard to the above revised objection, but deemed only partially persuasive with respect to claims 22-23 and 112-113 only. It is noted that the above objection was modified in response to applicant's amendment which added new claims 146 and 147. Applicant has failed to present a persuasive argument as to how a B-domainless generic claim is narrowed by dependent claims which encompass B-domain containing peptides.

Claim Rejections - 35 USC § 102

4. Claims 17, 27, 107 and 120 are rejected under 35 U.S.C. 102(b) as being anticipated by WPIDS English Abstract 88-362113 or EP 295597 (12/88) (which is attached for applicant's convenience).

The EP reference discloses a factor 8 derivative compound and its preparation in pharmaceuticals for treating hemophilia which lacks both the B domain and the vWF binding site (e.g. lacks 741-1689; wherein the B domain is 741-1648 and the vWF binding site is 1649-1689) and which possesses a mutated Arg-740 which acts an amino acid sequence spacer which connects the A1-A2 segment to the C1-C2 segment. The reference further discloses that "the new

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protein possesses a rapid activation by thrombin aside from a procoagulation activity that is very similar to one of the authentic protein and biologic half-value time” (e.g. see translation at page 2, lines 9-12). Thus the reference protein is stable and possesses a good specific activity. Accordingly, the reference meets the critical chemical claim limitations (e.g. absence of a B domain and Vwf binding site; and presence of a linking amino acid) and possesses improved properties and thus would be expected to “inherently” possess the same conformational structure upon thrombin activation as presently claimed. See MPEP 2112.02 and *In re Spada*, 15 USPQ2d 1655,1658 (Fed. Cir. 1990)(“Products of identical chemical composition can not have mutually exclusive properties”). The Examiner lacks the facilities to test the reference protein to see if it meets functional limitations; thus placing the burden directly on applicant (e.g. See *In re Brown*, 173 USPQ 685,688 (CCPA 1972)).

Discussion

Applicant’s arguments directed to the above rejection were considered but deemed nonpersuasive for the following reasons. Initially it is noted that the above rejection was modified in response to applicant’s amendment. Applicant argues that the reference fails to disclose a “spacer”. However, the reference clearly teaches a protein which possesses a mutated Arg-740 which acts an amino acid sequence spacer which connects the A1-A2 segment to the C1-C2 segment. Thus, chemically the reference compound meets the presently claimed spacer limitation. Applicant argues that the reference fails to disclose both a mutation at Arg 740 and an amino acid sequence spacer. However, the reference clearly does teach a mutated Arg-740 which acts an

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amino acid sequence spacer which connects the A1-A2 segment to the C1-C2 segment.

Accordingly, the reference discloses a protein that contains all the elements of the presently claimed invention. The presently claimed invention does not preclude the interpretation that the mutated amino acid can also serve as the spacer. With regard to applicant's functional/conformational limitation language it is noted that functional activity would inherently flow from a compound that possesses chemical structure within the scope of the presently claimed invention; unless demonstrated otherwise. Accordingly, the above rejection, as modified, is hereby retained.

Claim Rejections - 35 USC § 103

5. Claims 17, 20-22, 27, 107, 110-112, 120, 146 and 147 are rejected under 35 U.S.C. 103(a) as being unpatentable over WPIDS Abstract 88-362113 of EP 295597 (or translation thereof) (12/88) and Kaufman et al., U.S. Pat. No. 5,451,521 (9/95)..

The EP reference discloses a factor 8 derivative compound and pharmaceuticals for treating hemophilia which lacks both the B domain and the vWF binding site (e.g. lacks 741-1689; wherein the B domain is 741-1648 and the vWF binding site is 1649-1689) and which possesses a mutated Arg-740 which acts an amino acid sequence spacer which connects the A1-A2 segment to the C1-C2 segment. The EP reference differs from the presently claimed invention by failing to recite the Arg-740 mutation (e.g. Arg to Ala) and the use of a spacer which comprises a B-domain peptide.

However, the Kaufman reference discloses the making of procogulant factor VIII derivatives of formula A-X-B wherein A is 1-372 and B is 1690-2332 and X is a linking moiety which may comprise 0-1316 amino acids especially those amino acids selected from the sequence Arg-372 to Ser-1690 with a preferred embodiment incorporating Arg 372-Arg740 (e.g. see col. 8-9). Thus, Kaufman provides motivation to the skilled artisan to attach the A1-A2 heavy chain fragment to the light chain C1-C2 fragment utilizing amino acid linkers derived from the B chain of any length; of which is not critical. The Kaufman reference further teaches the replacement of Arg residues at position 740 (e.g. see Abstract) with non-conservative amino acid substitutions, including Ile, in order to obtain proteolytic resistance (e.g. see col. 2, lines 40-67 and Table II in

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col. 9). Accordingly, the substitution of Arg 740 with other nonconservative amino acids which possess similar side chain properties to Ile (e.g. aliphatic non-charged e.g. nonpolar), such as alanine or valine would have been obvious to one of ordinary skill in the art who wishes to obtain further proteolytic resistant derivatives. Thus, the modification of the EP reference peptide to incorporate a linking peptide which comprises B-chain residues and the further substitution of Arg with aliphatic non-charged amino acid residues (e.g. Ile, Val or Ala) would have been obvious in view of the teaching of the Kaufman reference to use such modifications in order to make procoagulant proteins.

Accordingly, the EP reference combined with the Kaufman reference render obvious proteins within the scope of the presently claimed invention. Accordingly, the above reference(s) meet the critical chemical claim limitations (e.g. absence of a B domain and Vwf binding site; and presence of a linking amino acid) and possesses improved properties and thus would be expected to possess the same conformational structure upon thrombin activation as presently claimed. See MPEP 2112.02 and *In re Spada*, 15 USPQ2d 1655,1658 (Fed. Cir. 1990) (“Products of identical chemical composition can not have mutually exclusive properties”). The Examiner lacks the facilities to test reference protein (s) to see if it meets functional limitations; thus placing the burden directly on applicant (e.g. See *In re Brown*, 173 USPQ 685,688 (CCPA 1972)).

Discussion

Applicant's arguments directed to the above obviousness rejection were considered but deemed nonpersuasive for the following reasons. The above rejection was modified in response to applicant's amendment (e.g. to encompass newly added claims). Applicant first intimates that the above 103 rejection somehow conflicts with the 102 rejection with regard to the sequence spacer. The Examiner disagrees since the claimed invention can be interpreted to encompass an Arg mutation which also serves as the spacer, or alternatively the presence of a spacer separate and apart from the “Arg” mutation. Applicant's argument that the references taken separately fail to render obvious the presently claimed invention, is not germane to the obviousness rejection above which is directed to the combined teaching of both references. Applicant fails to provide a

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reason why one of ordinary skill wouldn't combined the above two references to obtain multiple proteins species within the scope of the presently claimed invention. Applicant further argues that the references fail to teach functional/conformational characteristics of the protein upon thrombin activation. With regard to to applicant's functional/conformational limitation language it is noted that functional activity would necessarily flow from a compound that possesses chemical structure within the scope of the presently claimed invention; unless demonstrated otherwise. Accordingly, the above rejection, as modified, is hereby retained.

New Rejection

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 17 and 107 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (e.g. New Matter Rejection).

Applicant's newly added functional/conformational limitation is clearly broader than that described on page 9, line 6-11 which is limited to thrombin activation, with the further description of the covalent association of the A2 domain with the light chain..

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8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

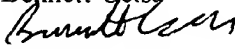
General information regarding further correspondence

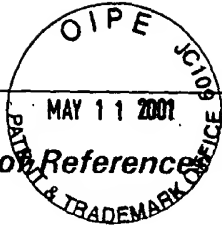
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Celsa whose telephone number is (703) 305-7556.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can be reached at (703)308-0254.

Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Bennett Celsa


June 27, 1999



Notice of References Cited

Application No.
08/980,038

Applicant(s)

Kaufman et al.

Examiner

Bennett Celsa

Group Art Unit
1654

Page 1 of 1

U.S. PATENT DOCUMENTS

	DOCUMENT NO.	DATE	NAME	CLASS	SUBCLASS
A					
B					
C					
D					
E					
F					
G					
H					
I					
J					
K					
L					
M					

FOREIGN PATENT DOCUMENTS

	DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUBCLASS
N						
O						
P						
Q						
R						
S						
T						

NON-PATENT DOCUMENTS

	DOCUMENT (Including Author, Title, Source, and Pertinent Pages)	DATE
U	English translation of EP 295597 A	6/88
V		
W		
X		



**UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office**

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

CORRECTED COPY *****

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/980038	11/26/97	KAUFMAN	R UMV-1184CP

DEANN F. SMITH, ESQ.
LAHIVE & COCKFIELD, LLP
28 STATE STREET
BOSTON, MA 02109

EXAMINER

CELSA, B

ART UNIT	PAPER NUMBER
1654	18

DATE MAILED:

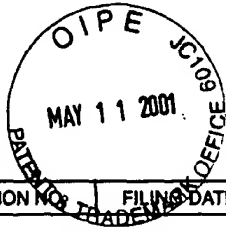
05/17/99

This is in response to the Power of Attorney filed 04/26/99

- ☐ 1. The Power of Attorney to you in this application **has been revoked** by the applicant. Future correspondence will be mailed to the new address of record. 37 CFR 1.33.
- ☐ 2. The Power of Attorney to you in this application **has been revoked** by the assignee who has intervened as provided by 37 CFR 3.71. Future correspondence will be mailed to the new address of record. (37 CFR 1.33).
- ☐ 3. The withdrawal as attorney in this application **has been accepted**. Future correspondence will be mailed to the new address of record. 37 CFR 1.33.

This is a communication from the
Patent and Trademark Office

- ☐ 4. The Power of Attorney in this application **is accepted**. Correspondence in this application will be mailed to the below-noted address as provided by 37 CFR 1.33.



UNITED STATES DEPARTMENT OF COMMERCE
Pat nt and Trad mark Office

Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO. <i>mk</i>
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08/980,038 11/26/97 KAUFMAN

R 2115001184US

EXAMINER

HM12/0414

HARNESS DICKEY & PIERCE
ATTORNEYS AND COUNSELORS
PO BOX 828
DUNFIELD HILLS NY 48300

CEL SA, R

ART UNIT

PAPER NUMBER

1554

DATE MAILED:

04/14/98

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

41155 001184 USB
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4/14/99

NON-RESPONSIVE AMEND.

Office Action Summary

MAY 11 2001

Application No.

08/980,038

Applicant(s)

Kaufman et al.

Examiner

Bennett Celsa

Group Art Unit

1654

☒ Responsive to communication(s) filed on Feb 4, 1999.

☐ This action is FINAL.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire one month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 17-23, 27, 32, 36, and 102-145 is/are pending in the application.

Of the above, claim(s) 18, 19, 32, 36, 102-106, 108, 109, 114-119, and 121-145 are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 17, 20-23, 27, 107, 110-113, and 120 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

Art Unit: 1654



Response to Amendment

1. The reply filed on 2/4/99 in paper no. 12 is not fully responsive to the prior Office action because of the following omission(s) or matter(s): the response fully addresses only Sequence Rule Compliance (the CRF was entered) and not the claim rejections e.g. items 5-12 of the office action mailed 1/21/99 in paper no. 11. See 37 CFR 1.111. Since the above-mentioned reply appears to be *bona fide*, applicant is given ONE (1) MONTH or THIRTY (30) DAYS (if applicable) from the mailing date of this notice, whichever is longer, within which to supply the omission or correction in order to avoid abandonment. **EXTENSIONS OF THIS TIME PERIOD MAY BE GRANTED UNDER 37 CFR 1.136(a) to more fully address the outstanding office action.**

General information regarding further correspondence

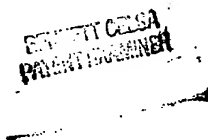
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Celsa whose telephone number is (703) 305-7556.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can be reached at (703) 308-0254.

Any inquiry of a general nature, or relating to the status of this application, should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Bennett Celsa

Bennett Celsa
April 12, 1999





Office No. UMV-1184CP

THE "RECEIVED" STAMP OF THE PATENT AND TRADEMARK OFFICE
IMPRINTED HEREON ACKNOWLEDGES THE FILING OF:

Description of Paper* and No.: Transmittal Letter for Amendment and Response (in duplicate); Amendment and Response (10 pages); Revocation of Prior Powers of Attorney and Appointment of New Power of Attorney; A check in the amount of \$18.00 (additional claim fee); and this return receipt postcard.

Title: *INACTIVATION RESISTANT FACTOR VIII*
Name of Applicant(s): Randal J. Kaufman et al.

Intf. or Serial No.: 08/980,038

Atty: DeAnna J. Smith, Esq.

Date: April 21, 1999



*with Certificate of First Class Mailing

In re the application of Randal J. Kaufman et al.

Case Docket No. UMV-1184CP

Serial No. 08/980,038

Filed: November 26, 1997

For: INACTIVATION RESISTANT FACTOR VIII

ASSISTANT COMMISSIONER FOR PATENTS

Washington, D.C. 20231

Sir:

Transmitted herewith for filing in connection with the above-identified application are the following:

- ☒ Amendment and Response (10 pages);
- ☒ Revocation of Prior Powers of Attorney and Appointment of New Power of Attorney; and
- ☒ Return receipt postcard.

The fee has been calculated as shown below:

(Col. 1)		(Col. 2)		(Col. 3)	SMALL ENTITY		OR	OTHER THAN A SMALL ENTITY	
	CLAIMS REMAINING AFTER AMENDMENT		HIGHEST NO. PREVIOUSLY PAID FOR	PRESENT EXTRA	RATE	ADDIT. FEE		RATE	ADDIT. FEE
TOTAL	* 14	MINUS	** 12	= 2	x 9 =	\$ 18.00		x 18 =	\$ 0.00
INDEP.	* 3	MINUS	*** 3	= 0	x 39 =	\$ 0.00		x 78 =	\$ 0.00
<input type="checkbox"/> FIRST PRESENTATION OF MULTIPLE DEP. CLAIM					+130 =	\$ 0.00		+ 260 =	\$ 0.00
					TOTAL	\$18.00	OR	TOTAL	\$0.00

- * If the entry in Col 1 is less than the entry in Col. 2, write "0" in Col. 3.
- ** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, write "20" in this space.
- *** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, write "3" in this space.

The "Highest Number Previously Paid For" (Total or Independent) is the highest number found from the equivalent box in Col. 1 of a prior amendment or the number of claims originally filed.

- ☒ A check in the amount of \$18.00 is enclosed for presentation of extra claims.
- ☐ A check in the amount of _____ is enclosed for .
- ☐ The Commissioner is hereby authorized to charge payment of the following fees associated with this communication or credit any overpayment to Deposit Account No. 12-0080. A duplicate copy of this sheet is enclosed.
 - ☐ Any filing fees under 37 CFR 1.16 for the presentation of extra claims.
 - ☐ Any patent application processing fees under 37 CFR 1.17.
- ☒ Please charge any additional fees or credit any overpayments associated with this communication to our Deposit Account No. 12-0080. A duplicate copy of this sheet is enclosed.

I hereby certify that this transmittal letter and the papers referred to as being enclosed therein are being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, DC 20231 on:

April 21, 1999

Date

Signature of Person Mailing

LAHIVE & COCKFIELD, LLP
Attorneys at Law

By DeAnn F. Smith
DeAnn F. Smith
Reg. No. 36,683
28 State Street
Boston, MA 02109
(617) 227-7400
Telecopier (617) 742-4214



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Randal J. Kaufman et al.

Serial No.: 08/980,038

Filed: November 26, 1997

For: INACTIVATION RESISTANT FACTOR VIII

Attorney Docket No.: UMV-1184CP

Group Art Unit: 1654

Examiner: B. Celsa

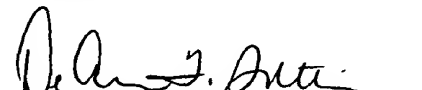
Assistant Commissioner for Patents
Washington, D.C. 20231

Certificate of First Class Mailing (37 CFR 1.8(a))

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April 21, 1999
Date of Signature and of Mail Deposit

By:


DeAnn F. Smith
Reg. No. 36,683
Attorney for Applicant

AMENDMENT AND RESPONSE

Dear Sir:

This is a response to the Office Action mailed from the Patent Office on January 21, 1999. In response to the Office Action, Applicants submit the following amendments and remarks.

In the claims:

Please add new claims 146-147 and amend claims 17, 21-23, 107 and 111-113, without prejudice, as follows:

17. (Amended) A procoagulant-active FVIII protein comprising a human FVIII polypeptide that is modified, wherein the modification comprises a deletion of the B domain, a deletion of the von Willebrand factor binding site, a mutation at Arg740 and an addition of an amino acid sequence spacer between the A2- and A3- domains[.], wherein the amino acid sequence spacer is of a sufficient length so that upon activation, the procoagulant-active FVIII protein becomes a heterodimer.

21. (Amended) The protein of Claim 17, wherein the amino acid sequence spacer is 54 amino acid residues in length.

22. (Amended) The protein of Claim 21, wherein the amino acid sequence spacer [comprises] consists of amino acid residues 741 to 794 of wild-type FVIII, wherein the amino acid residue at position 794 is selected from the group consisting of threonine and leucine.

23. (Amended) The protein of Claim 22, wherein the amino acid residue at position 794 is threonine.

107. (Amended) A procoagulant-active FVIII protein comprising a human FVIII polypeptide that is modified, wherein the modification consists of a deletion of the B domain, a deletion of the von Willebrand factor binding site, a mutation at Arg740 and an addition of an amino acid sequence spacer between the A2- and A3- domains[.], wherein the amino acid sequence spacer is of a sufficient length so that upon activation, the procoagulant-active FVIII protein becomes a heterodimer.

111. (Amended) The protein of Claim 107, wherein the amino acid sequence spacer is 54 amino acid residues in length.

112. (Amended) The protein of Claim 111, wherein the amino acid sequence spacer [comprises] consists of amino acid residues 741 to 794 of wild-type FVIII, wherein the amino acid residue at position 794 is selected from the group consisting of threonine and leucine.

113. (Amended) The protein of Claim 112, wherein the amino acid residue at position 794 is threonine.

146. (New) The protein of Claim 17, wherein the amino acid sequence spacer comprises amino acid residues 741 to 794 of wild-type FVIII, wherein the amino acid residue at position 794 is selected from the group consisting of threonine and leucine.

147. (New) The protein of Claim 107, wherein the amino acid sequence spacer comprises amino acid sequence spacer 741 to 794 of wild-type FVIII, wherein the amino acid residue at position 794 is selected from the group consisting of threonine and leucine.

REMARKS

In an effort to expedite prosecution of this application and in no way conceding the validity of the Examiner's position, Applicants have amended claims 17, 21-23, 107 and 111-113, without prejudice, to further define the present invention. In particular, Applicants have amended claims 17 and 107 to further define the amino acid sequence spacer. Applicants have amended claims 21-23 and 111-113 to add the term "amino acid" before the term "residues", and in claims 22 and 112, Applicants have replaced the term "comprises" with "consists of". Applicants have also added new claims 146 and 147. Support for the amendments and new claims may be found throughout the application as filed and in particular, without limitation, at page 9, lines 6-15. Claims 17, 20-23, 27, 107, 110-113, 120, 146 and 147 are new before the Examiner.

The claims of the present invention are drawn to inactivation resistant procoagulant-active FVIII proteins which, upon activation, become heterodimers. The novel proteins of the present invention comprise modified human FVIII polypeptide lacking the B domain and von Willebrand factor binding site and having a mutation at Arg740 and an addition of an amino acid sequence spacer between the A2- and A3- domains so that upon activation, a heterodimer is achieved. The heterodimer (novel FVIIIa) has an approximate five-fold increase in specific activity compared to purified wild-type FVIII which, upon activation, becomes a heterotrimer that is unstable and subject to rapid inactivation through disassociation of the A2 subunit. Novel, inactivation resistant procoagulant-active FVIII proteins are thus provided.

I. Election/Restriction

Applicants continue to traverse the restriction requirement set forth in the Office Action mailed September 30, 1998. In an effort to expedite prosecution, Applicants will continue to prosecute the Group III invention as defined by the Examiner. Pursuant to MPEP §821.04, Applicants request that upon allowance of a compound claim within the elected invention, the Examiner rejoin the method of use claims that are commensurate in scope with the allowed claims.

II. Sequence Rule Compliance

In response to the "Notice to Comply with the Sequence Listing", Applicants submitted on February 4, 1999 a Response to Notice to Comply and Statement in Support of Submission of Sequence Data with a hard-copy of the sequence listing and computer diskette.

III. Drawings

Applicants note the requirement of formal drawings and will submit same upon notice of allowance.

IV. 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claims 17, 20-23, 27, 107, 110-113 and 120 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In particular, the Examiner states that A) the phrase “procoagulant-active FVIII protein” in claims 17 and 107 is indefinite; B) the term “the B domain” in claims 17 and 107 lacks antecedent basis; C) the term “von Willebrand factor binding site” in claims 17 and 107 lacks antecedent basis; D) the term “the A2- and A3 – domains” in claims 17 and 107 lacks antecedent basis; E) the phrase “a mutation at Arg740” in claims 17 and 107 is unclear to the metes and bounds of “mutation”; F) the phrase “comprises residues 741 to 794 of wild-type factor FVIII” and “position 794...threonine” in claims 17 and 107 lacks antecedent basis; G) the term “comprises residues 741-794” in claims 22 and 112 is confusing as being dependent on claims 21 and 111 requiring a 54 amino acid residue spacer; and H) the term “residue(s)” in claims 21-23 and claims 111-113 should specify “amino acid residues”. The Examiner has also rejected claims 22, 23, 112 and 113 under 37 C.F.R. §1.75 as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicants respectfully traverse and request reconsideration.

With respect to rejection A), Applicants submit that the phrase “procoagulant-active FVIII protein” is clear and definite to one skilled in the art and, contrary to the Examiner’s assertion, after reading the specification, one skilled in the art would know the initial polypeptide structure for the claimed proteins. The specification describes

known DNA sequences encoding human FVIII and methods for modifying the known sequences to provide the claimed modified proteins. Applicants refer the Examiner to the specification at page 2, lines 5-19 and lines 25-30, page 10, lines 16-35 (and the references incorporated therein), page 11, lines 1-3 and 18-32, Example 3, and Figure 1A, for a detailed description of the procoagulant-active FVIII proteins of the present invention and methods of making same. Moreover, Applicant refers the Examiner to U.S. Patent No. 5,004,803 (incorporated by reference at page 10, line 29 of the present application) and U.S. Patent No. 5,451,521, which contain claim language similar to the now pending claims. Applicants submit that the structure of human FVIII is known in the art and, in addition, the specification describes in detail the structure of the modified human FVIII polypeptides as claimed. Applicants thus request withdrawal of the rejection.

With respect to rejections B) – D), the structure of human FVIII protein is well known to those skilled in the art and, as set forth above, is also set forth in the specification (see, *e.g.*, page 2, lines 5-35, page 10, lines 16-35 and the references incorporated therein, and Figure 1A). It is therefore unnecessary to reiterate the structure of human FVIII in order to define the modified, claimed human FVIII polypeptides. (Applicants again refer the Examiner to U.S. Patent No. 5,004,803 for accepted claim language). Applicants therefore request withdrawal of these rejections.

With respect to rejection E), Applicants submit that the phrase “a mutation at Arg740” is clear and definite and refer the Examiner to page 10, lines 25-26 of the specification, which describes a “mutation” as “any alteration including but not limited to substitutions, insertions and deletions.” Applicants further direct the Examiner to the Examples and in particular, Example 3 at page 22, lines 26-27, which describe an Arg740

mutation. Applicants thus submit that the claims as filed are clear and definite and request withdrawal of the rejection.

With respect to rejection F), independent claims 17 and 107 state that the modification in the human FVIII polypeptide comprises/consists of “a deletion of the B domain...and an addition of an amino acid sequence spacer.” Claims 22-23 and 112-113, which are dependent upon claims 17 and 107, respectively, further define the additional amino acid sequence spacer. Thus, the claimed human FVIII although B-domainless, may contain an additional amino acid sequence that happens to have a sequence that is identical to a portion of the B domain. Applicants thus submit that the claims are clear and definite with respect to these modifications and request withdrawal of the rejection.

With respect to rejections G), H) and the rejection under 37 C.F.R. § 1.75(c), Applicants have amended claims 21-23 and 111-113 to add the phrase “amino acid” before the word “residues” and, in claims 22 and 112, Applicants have substituted the term “comprises” with “consists of”. Applicants submit that these amendments render the rejections moot and therefore request withdrawal of the rejections.

V. 35 U.S.C. §102(b)

The Examiner has rejected claims 17, 27, 107 and 120 under 35 U.S.C. §102(b) as being anticipated by WPIDS English Abstract 88-362113 of European Application No. 295597 (“EP abstract”). The Examiner states that the EP abstract discloses a FVIII derivative compound which lacks the B domain and the VWF binding site and which possesses a mutated Arg740 which acts as an amino acid sequence spacer. Applicants respectfully traverse and request reconsideration.

The EP abstract describes a FVIII derivative that lacks the 741-1689 amino acid region of the native protein and has “a new site at Arg-740”. The claimed procoagulant-active FVIII proteins comprise a modified human FVIII polypeptide also having a mutation at Arg740 “and an addition of an amino acid sequence spacer”. The EP abstract does not disclose or suggest an amino acid sequence spacer. Moreover, the Examiner’s assertion that a mutated Arg740 “acts as an amino acid sequence spacer”, is clearly without merit when the present claims recite both a mutation at Arg740 and an amino acid sequence spacer. Applicants submit that the Examiner is improperly reconstructing the EP abstract in light of the present invention, to include elements that are taught by the present invention but are clearly not disclosed or suggested by the EP abstract.

Moreover, in an effort to expedite prosecution of this application and in no way conceding the validity of the Examiner’s arguments, Applicants have amended the claims to further define the amino acid sequence spacer as “of a sufficient length so that upon activation, the procoagulant-active FVIII protein becomes a heterodimer.” Clearly the EP abstract does not teach or suggest such a protein. Applicants thus request withdrawal of the rejection.

VI. 35 U.S.C. § 103

The Examiner has rejected claims 17, 20-22, 27, 107, 110-112 and 120 under 35 U.S.C. §103(a) as being unpatentable over the EP abstract and U.S. Patent No. 5,451,521 (“‘521 patent”). The Examiner states that the EP abstract teaches a FVIII derivative compound that lacks the B domain and the VWF binding site and which possesses a mutated Arg740. The Examiner asserts that the EP abstract differs from the claimed invention by failing to recite the Arg740 mutation (Arg to Ala) and the use of a spacer. (Query whether the above §102(b) rejection is therefore appropriate.) The Examiner states that the ‘521 patent discloses procoagulant factor FVIII derivatives of the formula

A-x-B, wherein A is amino acid residues 1-372 of human FVIII, B is amino acid residues 1690-2332 of human FVIII and x is a linking moiety. The Examiner then states that the '521 patent provides motivation to attach the A1-A2 heavy chain fragment to the C1-C2 light chain fragment utilizing amino acid linkers derived from the B chain. The Examiner also states that the '521 patent teaches the replacement of the Arg residue at position 740 with non-conservative amino acid substitutions such as Ile, in order to obtain proteolytic resistance and thus substitution of Arg740 with other non-conservative amino acids which possess similar side chain properties to Ile, would have been obvious. The Examiner then asserts that modifying the EP abstract to incorporate a linking peptide which comprises B-chain residues and the further substitution of Arg, would have been obvious in view of the '521 patent. Applicants respectfully traverse and request reconsideration.

As set forth above and admitted by the Examiner, the EP abstract does not disclose or suggest an amino acid sequence spacer and thus does not disclose or suggest the claimed protein. With respect to the '561 patent, it discloses a protein characterized by the amino acid sequence A-x-B, wherein A represents A1a-1 through Arg-372 and B represents Ser-1690 through Tyr-2332 of human FVIII, and x represents 0-1316 amino acids substantially duplicative of Arg-372 through Ser-1690 of a full-length sequence of FVIII. Neither reference, either alone or in combination, teach or suggest a procoagulant-active FVIII protein comprising a human FVIII polypeptide that is modified, wherein the modification comprises a mutation at Arg 740 and an addition of an amino acid sequence spacer. Likewise, neither reference, either alone or in combination, teach or suggest a procoagulant-active FVIII protein that upon activation by thrombin achieves a heterodimer, let alone the now claimed procoagulant-active FVIII protein having an amino acid sequence spacer between the A2- and A3- domains, wherein the amino acid sequence spacer is of a sufficient length so that upon activation,

the procoagulant-active FVIII protein becomes a heterodimer. The claims as amended are thus not taught or suggested by the prior art and thus Applicants request withdrawal of the rejection.

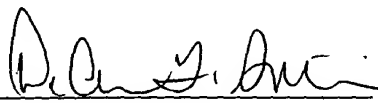
Again, no concession is made to the validity of the Examiner's rejections and Applicants' remarks made herein are for purposes of further clarifying for the Examiner Applicants position so that upon further examination it will be clear to the Examiner that the claimed invention, from the outset, is patentable. There is no intention to surrender any range of equivalents by the remarks made herein. The remarks are made in the interest of orderly prosecution and to secure expedited allowance of the application.

SUMMARY

The claims are believed to be in condition for allowance, and such action is respectfully requested. If a telephone conversation with Applicants' representative would expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' representative at (617) 227-7400.

Date: April 21, 1999

LAHIVE & COCKFIELD, LLP
Attorneys at Law

By 
DeAnn F. Smith
Reg. No. 36,683
28 State Street
Boston, MA 02109
(617) 227-7400
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Re the application of: Randal J. Kaufman et al.

Serial No.: 08/980,038

Filed: November 26, 1997

For: INACTIVATION RESISTANT FACTOR VIII

Attorney Docket No.: UMV-1184CP

Group Art Unit: 1654

Examiner: B. Celsa

Assistant Commissioner for Patents
Washington, D.C. 20231

Certificate of First Class Mailing (37 CFR 1.8(a))

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on the date set forth below.

April 21, 1999
Date of Signature and of Mail Deposit

By:

DeAnn Smith
DeAnn Smith
Reg. No. 36,683
Attorney for Applicant

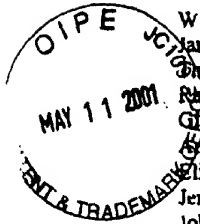
REVOCATION OF PRIOR POWERS OF ATTORNEY
AND APPOINTMENT OF NEW POWER OF ATTORNEY

Dear Sir:

The Regents of the University of Michigan, the Assignee of the entire right, title and interest in the above-identified application by virtue of the Assignment document recorded in the U.S. Patent and Trademark Office hereby revokes all Powers of Attorney with respect to that application and appoints the below listed attorneys with full power of substitution and revocation to prosecute this application and to transact all business in the Patent Office connected therewith.

U.S.S.N. 08/980,038

Group Art L. 1654



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Reg. No. 38,220
Reg. No. 38,872
Reg. No. 17,425
Reg. No. 36,683

Lawrence E. Monks
David A. Lane, Jr
Catherine J. Kara
Linda M. Chinn
Kevin J. Canning
Faustino A. Lichauco
Jeanne M. DiGiorgio
Megan E. Williams
Nicholas P. Triano III
Peter C. Lauro
Reza Mollaaghababa
Timothy J. Douros
John L. Welch
William D. DeVaul

Reg. No. 34,224
Reg. No. 39,261
Reg. No. P41,106
Reg. No. 31,240
Reg. No. 35,470
Reg. No. 41,942
Reg. No. 41,710
Reg. No. 43,270
Reg. No. 36,397
Reg. No. 32,360
Reg. No. 43,810
Reg. No. 41,716
Reg. No. 28,129
Reg. No. 42,483

of LAHIVE & COCKFIELD, LLP, 28 State Street, Boston, Massachusetts 02109,
United States of America.

Please send all correspondence relating to the above patent application to:

DeAnn F. Smith, Esq.
LAHIVE & COCKFIELD, LLP
28 State Street
Boston, MA 02109
(617) 227-7400

THE REGENTS OF THE UNIVERSITY OF MICHIGAN

By: Marvin G. Parnes

Marvin G. Parnes, Assistant Vice President for Research and
Interim Director, Technology Management Office

Dated: 4-20-99



Interview Summary

Application No.

08/980,038

Applicant(s)

Kaufman et al.

Examiner

Bennett Celsa

Group Art Unit

1627

All participants (applicant, applicant's representative, PTO personnel):

(1) Bennett Celsa

(3) _____

(2) DeAnn F. Smith

(4) _____

Date of Interview Nov 15, 2000

Type: ☐ Telephonic ☒ Personal (copy is given to ☐ applicant ☒ applicant's representative).

Exhibit shown or demonstration conducted: ☐ Yes ☒ No. If yes, brief description:

Agreement ☐ was reached. ☒ was not reached.

Claim(s) discussed: of record

Identification of prior art discussed:

of record

Description of the general nature of what was agreed to if an agreement was reached, or any other comments:

Applicant's representative will consider filing a response after final presenting traversal of rejection and amended claims in order to attempt to overcome the outstanding issues of record.

(A fuller description, if necessary, and a copy of the amendments, if available, which the examiner agreed would render the claims allowable must be attached. Also, where no copy of the amendments which would render the claims allowable is available, a summary thereof must be attached.)

1. ☒ It is not necessary for applicant to provide a separate record of the substance of the interview.

Unless the paragraph above has been checked to indicate to the contrary, A FORMAL WRITTEN RESPONSE TO THE LAST OFFICE ACTION IS NOT WAIVED AND MUST INCLUDE THE SUBSTANCE OF THE INTERVIEW. (See MPEP Section 713.04). If a response to the last Office action has already been filed, APPLICANT IS GIVEN ONE MONTH FROM THIS INTERVIEW DATE TO FILE A STATEMENT OF THE SUBSTANCE OF THE INTERVIEW.

2. ☐ Since the Examiner's interview summary above (including any attachments) reflects a complete response to each of the objections, rejections and requirements that may be present in the last Office action, and since the claims are now allowable, this completed form is considered to fulfill the response requirements of the last Office action. Applicant is not relieved from providing a separate record of the interview unless box 1 above is also checked.

Examiner Note: You must sign and stamp this form unless it is an attachment to a signed Office action.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



In re the application of: Randal J. Kaufman, et al.

Serial No.: 08/980,038

Filed: November 26, 1997

For: *INACTIVATION RESISTANT FACTOR VIII*

Attorney Docket No.: UMV-1184CPCPA

Group Art Unit: 1654

Examiner: Celsa, B.

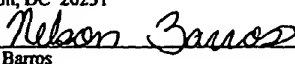
BOX CPA
Commissioner for Patents
Washington, D.C. 20231

REQUEST FOR THREE-MONTH EXTENSION OF TIME

Dear Sir:

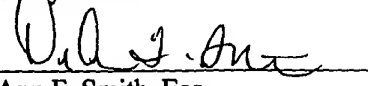
Applicants request a three-month extension of time pursuant to 37 CFR 1.136(a) in which to respond to the outstanding Final Office Action dated October 11, 2000. In lieu of a response, a Continued Prosecution Application (CPA) is being filed concurrently.

Enclosed is a check which covers the appropriate fee of \$445.00 based on small entity status. Please charge any underpayments or credit any overpayments to our Deposit Account No. 12-0080. A duplicate of this sheet is enclosed.

"Express Mail" mailing label number	EL 745 889 166 US
Date of Deposit	April 11, 2001
I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to BOX CPA, Commissioner for Patents, Washington, DC 20231	
	
Nelson F. Barros	
Please Print Name of Person Signing	

Dated: April 11, 2001

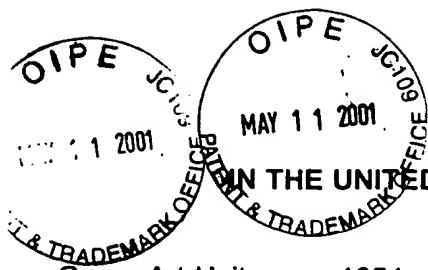
LAHIVE & COCKFIELD, LLP
Attorneys at Law

By 
DeAnn F. Smith, Esq.
Registration No. 36,683
28 State Street
Boston, MA 02109
Telephone - 617-227-7400
Facsimile - 617-742-4214



Applicant: Randall J. Kaufman et al.	Case No.: 21155-001184USB
Serial No.: 08/980,038	Filing Date: November 26, 1997
Title: Inactivation Resistant Factor VIII	

Please acknowledge receipt of: Response To Notice To Comply (in duplicate); Second Preliminary Amendment (with attached Sequence Listing (2 pages)); Statement In Support Of Submission Of Sequence Data (including hard copy of Sequence Listing and computer diskette); Copy of Notice To Comply - Certificate of Mailing.		
by stamping and return to Harness, Dickey & Pierce, P.L.C.		
Due: February 21, 1999	Attorney: DFS	USPTO Date Stamp



PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket: 2115S-001184USB

Group Art Unit: 1654)
Examiner: B. Celsa)
Inventor(s): Randal J. Kaufman et al.)
Serial No.: 08/980,038)
Filed: November 26, 1997)
For: Inactivation Resistant)
Factor VIII)

RESPONSE TO NOTICE
TO COMPLY

DT
3-4-99 PC

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231 on February 4, 1999.

By DeAnn F. Smith

Hon. Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

In response to the Notice to Comply with Requirements for Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures (copy enclosed) mailed January 21, 1999, for which the one-month shortened statutory period for response is set to expire February 21, 1999, enclosed herewith is a Statement in Support of Submission of Sequence Data with hard-copy of Sequence Listing and computer diskette and a Second Preliminary Amendment with attached Sequence Listing.

If for some reason, Applicants have not paid a sufficient fee to prevent the abandonment of this application, please charge Deposit Account No. 08-0750 for any further fees which may be due. A duplicate copy of this sheet is enclosed.

Respectfully submitted,

Dated: 2/4/99

By: DeAnn F. Smith
DeAnn F. Smith
Attorney For Applicants
Reg No. 36,683

Harness, Dickey & Pierce, P.L.C.
P.O. Box 828
Bloomfield Hills, Michigan 48303
(248) 641-1600
DFS/gmp



PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket: 2115S-001184USB

Art Unit: 1654)
Examiner: B. Celsa)
Inventors: Randal J. Kaufman, et al.)
Serial No. 08/980,038)
Filed: November 26, 1997)
For: Inactivation Resistant)
Factor VIII)

STATEMENT IN SUPPORT
OF SUBMISSION OF
SEQUENCE DATA

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231 on February 4, 1999.

By DeAnn F. Smith

Commissioner of Patents and Trademarks
Washington, D.C. 20231

Dear Sir:

I, DeAnn F. Smith, am an attorney with the firm of Harness, Dickey and Pierce, P.L.C., counsel for Applicants in the above-entitled application and am registered to practice before the United States Patent and Trademark Office.

I hereby state that the content of the computer readable form (diskette) is the same as the paper copy of the Sequence Listing, which are both submitted herewith.

Respectfully submitted,

Dated: 2/4/99

By: DeAnn F. Smith
DeAnn F. Smith
Reg No. 36,683

Harness, Dickey & Pierce, P.L.C.
P.O. Box 828
Bloomfield Hills, Michigan 48303
(248) 641-1600

DFS/gmp
Enclosures



1

SEQUENCE LISTING

<110> Kaufman, Randal J
Pipe, Steven W
Amano, Kagehiro

<120> Inactivation Resistant Factor VIII

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<141> 1997-11-26

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1 5 10 15

Leu Leu Phe Cys His Ile Ser Ser
20

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket: 2115S-001184USB

Art Unit: 1654)
Examiner: B. Celsa)
Inventors: Randal J. Kaufman, et al.)
Serial No. 08/980,038)
Filed: November 26, 1997)
For: Inactivation Resistant)
Factor VIII)

**SECOND
PRELIMINARY AMENDMENT**

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Commissioner of Patents and Trademarks, Washington, D.C. 20231 on February 4, 1999.

By Dea J. Sullivan

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Dear Sir:

Please amend the above-identified application as follows:

IN THE SPECIFICATION:

Please amend the specification as follows:

Page 7, line 19, after "FVIII" insert --(SEQ ID NO: 3)--.

Page 23, line 2, after "threonine" insert --(SEQ ID NOS: 1 and 2)--.

REMARKS

In response to the Notice to Comply with Requirements for Patent Applications
Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures mailed January


Attorney Docket: 2115S-001184USB
Serial No. 08/980,038

21, 1999, Applicants have amended the Sequence Listing to comply with 37 C.F.R. 1.821-1.825. The specification has also been amended to reflect the SEQ ID NOS. The Sequence Listing submitted herewith contains no new matter.

Applicants respectfully submit that the application now stands ready and in condition for allowance and such allowance is courteously solicited. Should the Examiner have any questions or wish to further discuss this matter, it is requested that the undersigned attorney be contacted at (248) 641-1600.

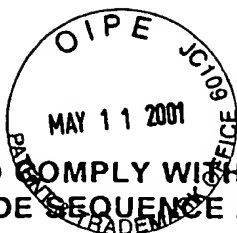
Respectfully submitted,

Dated: 2/4/99

By: 
DeAnn F. Smith
Reg No. 36,683

Harness, Dickey & Pierce, P.L.C.
P.O. Box 828
Bloomfield Hills, Michigan 48303
(248) 641-1600

DFS/gmp



Application No. 08/980,035

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 CFR 1.821 - 1.825 for the following reason(s):

- ☒ 1. This application clearly fails to comply with the requirements of 37 CFR 1.821 - 1.825. Applicant's attention is directed to these regulations, published at 1114 OG 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.
- ☒ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 CFR 1.821(c).
- ☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 CFR 1.821(e).
- ☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 CFR 1.822 and/or 1.823, as indicated on the attached marked-up copy of the "Raw Sequence Listing."
- ☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A substitute computer readable form must be submitted as required by 37 CFR 1.825(d).
- ☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 CFR 1.821(e).
- ☐ 7. Other: _____

Applicant must provide:

- ☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing"
- ☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification
- ☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d)

For questions regarding compliance with these requirements, please contact:

For Rules Interpretation, call (703) 308-1123
For CRF submission help, call (703) 308-4212
For PatentIn software help, call (703) 308-6856

Please return a copy of this notice with your response. _____